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Madsen BK, Zetner D, Møller AM, Rosenberg J

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[Intervention Review]

Melatonin for preoperative and postoperative anxiety in adults

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ABSTRACT

Background

Anxiety in relation to surgery is a well-known problem. Melatonin offers an alternative treatment to benzodiazepines for ameliorating this condition in the preoperative and postoperative periods.

Objectives

To assess the effects of melatonin on preoperative and postoperative anxiety compared to placebo or benzodiazepines.

Search methods

We searched the following databases on 10 July 2020: CENTRAL, MEDLINE, Embase, CINAHL, and Web of Science. For ongoing trials and protocols, we searched clinicaltrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform.

Selection criteria

We included randomized, placebo-controlled or standard treatment-controlled (or both) studies that evaluated the effects of preoperatively administered melatonin on preoperative or postoperative anxiety. We included adult patients of both sexes (15 to 90 years of age) undergoing any kind of surgical procedure for which it was necessary to use general, regional, or topical anaesthesia.

Data collection and analysis

One review author conducted data extraction in duplicate. Data extracted included information about study design, country of origin, number of participants and demographic details, type of surgery, type of anaesthesia, intervention and dosing regimens, preoperative anxiety outcome measures, and postoperative anxiety outcome measures.

Main results

We included 27 randomized controlled trials (RCTs), involving 2319 participants, that assessed melatonin for treating preoperative anxiety, postoperative anxiety, or both.

Twenty-four studies compared melatonin with placebo. Eleven studies compared melatonin to a benzodiazepine (seven studies with midazolam, three studies with alprazolam, and one study with oxazepam). Other comparators in a small number of studies were gabapentin, clonidine, and pregabalin.

No studies were judged to be at low risk of bias for all domains. Most studies were judged to be at unclear risk of bias overall. Eight studies were judged to be at high risk of bias in one or more domain, and thus, to be at high risk of bias overall.

Melatonin versus placebo

Melatonin probably results in a reduction in preoperative anxiety measured by a visual analogue scale (VAS, 0 to 100 mm) compared to placebo (mean difference (MD) -11.69, 95% confidence interval (CI) -13.80 to -9.59; 18 studies, 1264 participants; moderate-certainty evidence), based on a meta-analysis of 18 studies.

Melatonin may reduce immediate postoperative anxiety measured on a 0 to 100 mm VAS compared to placebo (MD -5.04, 95% CI -9.52 to -0.55; 7 studies, 524 participants; low-certainty evidence), and may reduce delayed postoperative anxiety measured six hours after surgery using the State-Trait Anxiety Inventory (STAI) (MD -5.31, 95% CI -8.78 to -1.84; 2 studies; 73 participants; low-certainty evidence).

Melatonin versus benzodiazepines (midazolam and alprazolam)

Melatonin probably results in little or no difference in preoperative anxiety measured on a 0 to 100 mm VAS (MD 0.78, 95% CI -2.02 to 3.58; 7 studies, 409 participants; moderate-certainty evidence) and there may be little or no difference in immediate postoperative anxiety (MD -2.12, 95% CI -4.61 to 0.36; 3 studies, 176 participants; low-certainty evidence).

Adverse events

Fourteen studies did not report on adverse events. Six studies specifically reported that no side effects were observed, and the remaining seven studies reported cases of nausea, sleepiness, dizziness, and headache; however, no serious adverse events were reported. Eleven studies measured psychomotor and cognitive function, or both, and in general, these studies found that benzodiazepines impaired psychomotor and cognitive function more than placebo and melatonin. Fourteen studies evaluated sedation and generally found that benzodiazepine caused the highest degree of sedation, but melatonin also showed sedative properties compared to placebo. Several studies did not report on adverse events; therefore, it is not possible to conclude with certainty, from the data on adverse effects collected in this review, that melatonin is better tolerated than benzodiazepines.

Authors' conclusions

When compared with placebo, melatonin given as premedication (as tablets or sublingually) probably reduces preoperative anxiety in adults (measured 50 to 120 minutes after administration), which is potentially clinically relevant. The effect of melatonin on postoperative anxiety compared to placebo (measured in the recovery room and six hours after surgery) was also evident but was much smaller, and the clinical relevance of this finding is uncertain. There was little or no difference in anxiety when melatonin was compared with benzodiazepines. Thus, melatonin may have a similar effect to benzodiazepines in reducing preoperative and postoperative anxiety in adults.

PLAIN LANGUAGE SUMMARY

Melatonin for preoperative and postoperative anxiety in adults

Review question

We reviewed the evidence from randomized controlled trials about the effects of melatonin on preoperative and postoperative anxiety in adults undergoing surgery when compared with placebo or benzodiazepine sedative drugs.

Background

People often feel uneasy and apprehensive both before and after surgery. Anxiety occurs in up to 80% of individuals undergoing surgery. They may be concerned about their illness, the need for hospitalization and being incapacitated, anaesthesia, surgery, pain, and the situation.

Factors that can influence risk of anxiety include age (younger age), being female, surgery type, type of anaesthesia, and cultural and religious differences. Being anxious can lead to increased pain and the need for additional pain management.

Interventions to reduce the level of anxiety include anxiolytic-sedative drugs such as benzodiazepines, information and effective communication around the time of surgery, cognitive-behavioural therapy, music, and massage therapy.

Benzodiazepines can cause cognitive problems such as trouble remembering and concentrating and daytime sleepiness, and they can interfere with coordination and physical movement, even after single doses.

Melatonin is a hormone produced in the pineal gland in the brain that regulates circadian rhythms. These are the body and behavioural changes that follow a daily cycle and help to determine sleep patterns. Studies have shown that melatonin can reduce anxiety. It causes few or no cognitive problems and has no known serious side effects. This means it could be a worthy alternative to medical treatment.

Search date

Evidence for this review update is current to July 2020.

Study characteristics

We found 27 randomized studies involving 2319 adult participants that looked at the effects of melatonin given before surgery on the level of anxiety both before and after surgery. Most studies were conducted in developing countries. We included any kind of surgical procedure in which general, regional, or topical anaesthesia was used.

Melatonin doses varied from 3 to 10 mg or from 0.05 to 0.4 mg/kg. Benzodiazepine (midazolam, oxazepam, or alprazolam) doses ranged from 0.25 to 15 mg or from 0.05 to 0.2 mg/kg.

None of the studies reported receipt of funding from drug manufacturers or agencies with commercial interests.

Key results

Twenty-four studies compared melatonin with placebo, and 11 studies compared melatonin with benzodiazepine drugs. Gabapentin, pregabalin, and clonidine were also compared with melatonin in some studies.

Melatonin reduced anxiety before surgery when compared to placebo (18 studies, 1264 participants; moderate-certainty evidence).

The reduction in anxiety after surgery was small compared with that seen with placebo (7 studies, 524 participants; low-certainty evidence), including at six hours after surgery (2 studies, 73 participants; low-certainty evidence).

Melatonin may have similar effects to benzodiazepines on the level of anxiety before surgery (7 studies, 409 participants; moderate-certainty evidence) and immediately after surgery (3 studies, 176 participants; low-certainty evidence).

Fourteen studies did not report on adverse events, six studies reported that no side effects were observed, and seven studies reported cases of nausea, sleepiness, dizziness, and headache. Benzodiazepines interfered with psychomotor and cognitive function more than placebo and melatonin (in 11 studies). They caused the greatest degree of sedation, although melatonin also showed sedation compared to placebo (14 studies). No serious adverse events were reported.

Quality of the evidence

We are moderately confident that melatonin reduces anxiety preoperatively compared with placebo. Effects on immediate and delayed postoperative anxiety after surgery are less clear when compared with placebo (low-quality evidence).

We did not find any evidence that melatonin differs in antianxiety effects from benzodiazepines (moderate- and low-quality evidence).

It remains unclear whether the anxiety-reducing effects of melatonin apply to all surgical patients.

Conclusions

Giving melatonin before surgery may effectively reduce anxiety before surgery, but any reduction in anxiety after surgery with melatonin is less clear when compared with placebo.

SUMMARY OF FINDINGS

Summary of findings 1. Summary of findings

Melatonin compared with placebo

Patient or population: patents undergoing elective surgery

Setting: hospital

Intervention: melatonin

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Melatonin				
Preoperative anxiety (VAS) VAS (0 to 100 mm) measured approximately 50 to 120 minutes after premedication 0: no anxiety 100: maximum anxiety possible	Mean VAS total ranged across control groups from **22.7 to 66.5,** and mean change in VAS ranged across control groups from **4 to -22**	Mean VAS in intervention groups was **11.69 lower** (13.80 lower to 9.59 lower) Lower score indicated less preoperative anxiety compared to placebo		1264 (18 studies)	⊕⊕⊕⊖ **Moderate**[a]	Melatonin most likely decreases preoperative anxiety compared with placebo
Preoperative anxiety (STAI) STAI (20 to 80) measured approximately 120 minutes after premedication 20: no anxiety 80: maximum anxiety possible	Mean STAI in control group measured just before entrance to the operating room was **39.73**	Mean STAI in intervention group measured just before entrance to the operating room was **41.18**		44 (1 study)	⊕⊖⊖⊖ **Very low** [b]	Because only 1 study examined preoperative anxiety using an STAI, no meta-analysis was performed
Preoperative anxiety (6-item STAI) STAI 6-item (6 to 24) measured approximately 90 minutes after premedication	Mean STAI in control group measured at patient arrival to the operating room was **13.5**	Mean STAI in intervention group measured at patient arrival to the operating room was **11.6**		36 (1 study)	⊕⊕⊖⊖ **Low** [c]	Because only 1 study examined preoperative anxiety using a 6-item STAI, no meta-analysis was performed

6: no anxiety 24: maximum anxiety possible					
Immediate postoperative anxiety (VAS) VAS (0 to 100 mm) measured after surgery, in recovery, or at discharge from recovery room 0: no anxiety 100: maximum anxiety possible	Mean VAS total ranged across control groups from**0 to 48,** and mean change in VAS ranged across control groups from **-4.7 to -6.5**	Mean VAS in intervention groups was **5.04 lower** (9.52 lower to 0.55 lower) Lower score indicated less postoperative anxiety compared to placebo	524 (7 studies)	⊕⊕⊖⊖ **Low** [d]	Melatonin may have an effect on postoperative anxiety compared with placebo; however, this effect was below the minimum clinical effect
Delayed postoperative anxiety (STAI) STAI (20 to 80) measured 6 hours after surgery 20: no anxiety 80: maximum anxiety possible	Mean STAI ranged across control groups from **42.2 to 42.5**	Mean STAI in intervention groups was **5.31 lower** (8.78 lower to 1.84 lower) Lower score indicated less postoperative anxiety compared to placebo	73 (2 studies)	⊕⊕⊖⊖ **Low** [e]	Melatonin may have an effect on postoperative anxiety compared with placebo; however, this effect was below the minimum clinical effect
Postoperative anxiety **(6-item STAI)** STAI 6-item (6 to 24) measured 1 hour and 6 hours after surgery 6: no anxiety 24: maximum anxiety possible	Mean STAI value in control group 1 hour after surgery was **11** Mean STAI value in control group 6 hours after surgery was **11.6**	Mean STAI value in melatonin group 1 hour after surgery was **8** Mean STAI value in melatonin group 6 hours after surgery was **7.9**	36 (1 study)	⊕⊕⊖⊖ **Low** [f]	Because only 1 study examined preoperative anxiety using a 6-item STAI, no meta-analysis was performed

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; STAI: State-Trait Anxiety Inventory; VAS: visual analogue scale.

GRADE Working Group grades of evidence.
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[a]The certainty of evidence was downgraded by one level due to unclear overall risk of bias and the presence of substantial heterogeneity. We chose not to downgrade by two levels because sensitivity analysis excluding all studies with high risk of bias showed a similar effect estimate; we therefore concluded that high risk of bias in the included studies did not affect conclusions.

[b]We chose to downgrade the evidence by three levels due to imprecision and high risk of bias: only one study with 44 participants examined preoperative anxiety using STAI; this study also had overall high risk of bias.

[c]We chose to downgrade the evidence by two levels due to imprecision: only one study with 36 participants examined preoperative anxiety using a six-item STAI.

[d]The certainty of evidence was downgraded by two levels due to large heterogeneity of the studies (I^2 = 89%) and overall high risk of bias. Several of the included studies had overall high risk of bias, making the overall risk of bias for the outcome high. When all studies with high risk of bias were excluded from the sensitivity analysis, the effect of the intervention was lost, which is why we suspect that inclusion of studies with overall high risk of bias may alter conclusions.

[e]The certainty of evidence was downgraded by two levels due to the small numbers of participants.

[f]The certainty of evidence was downgraded by two levels due to the small numbers of participants.

Summary of findings 2. Summary of findings

Melatonin compared with benzodiazepine

Patient or population: patients undergoing elective surgery

Setting: hospital

Intervention: melatonin

Comparison: benzodiazepine (midazolam, alprazolam)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Benzodiazepine	Melatonin				
Preoperative anxiety (VAS) VAS (0 to 100 mm) measured approximately 90 minutes after premedication 0: no anxiety 100: maximum anxiety possible	Mean VAS total ranged across control groups from **3.6 to 16.7,** and mean change in VAS ranged across control groups from **-7.7 to -50**	Mean VAS in intervention groups was **0.78 higher** (2.02 lower to 3.58 higher) A higher score indicated greater preoperative anxiety compared to benzodiazepine		409 (7 studies)	⊕⊕⊕⊖ **Moderate** [a]	Melatonin most likely has little or no effect on preoperative anxiety compared with benzodiazepines
Preoperative anxiety (STAI) STAI (20 to 80) 20: no anxiety	No studies available	No studies available	-	-	-	-

80: maximum anxiety possible						
Preoperative anxiety (6-item STAI) STAI 6-item (6 to 24) measured approximately 90 minutes after premedication 6: no anxiety 24: maximum anxiety possible	Mean STAI in benzodiazepine group measured at patient arrival to the operating room was **10.5**	Mean STAI in melatonin group measured at patient arrival to the operating room was **11.6**		35 (1 study)	⊕⊕⊖⊖ **Low** [b]	Because only 1 study examined preoperative anxiety using a 6-item STAI, no meta-analysis was performed
Immediate postoperative anxiety (VAS) VAS (0 to 100 mm) measured approximately 90 minutes after surgery or in recovery room 0: no anxiety 100: maximum anxiety possible	Mean VAS in control group was **7.4** and mean change in VAS ranged across control groups from **-5.3 to -6.4**	Mean VAS in intervention groups was **2.12 lower** (4.61 lower to 0.36 higher) Lower score indicated less postoperative anxiety compared to benzodiazepine		176 (3 studies)	⊕⊕⊖⊖ **Low** [c]	Melatonin had little or no effect on postoperative anxiety compared with benzodiazepines
Postoperative anxiety **(6-item STAI)** STAI 6-item (6 to 24) measured 1 hour and 6 hours after surgery 6: no anxiety 24: maximum anxiety possible	Mean STAI value in benzodiazepine group 1 hour after surgery was **10.4** Mean STAI value in benzodiazepine group 6 hours after surgery was **9.3**	Mean STAI value in melatonin group 1 hour after surgery was **8** Mean STAI value in melatonin group 6 hours after surgery was **7.9**		35 (1 study)	⊕⊕⊖⊖ **Low** [d]	Because only 1 study examined preoperative anxiety using a 6-item STAI, no meta-analysis was performed

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; STAI: State-Trait Anxiety Inventory; VAS: visual analogue scale.

GRADE Working Group grades of evidence.
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[a]The certainty of evidence was downgraded by one level due to high overall risk of bias for the outcome and substantial heterogeneity. We decided not to downgrade the evidence by two levels because sensitivity analysis excluding all studies with overall high risk of bias showed a similar effect estimate; we therefore concluded that high risk of bias in the included studies did not alter conclusions.

[b]We chose to downgrade the evidence by two levels because only one study with 35 participants examined preoperative anxiety using a six-item STAI.

[c]The certainty of evidence was downgraded by two levels due to the small numbers of participants. One study had overall high risk of bias, but sensitivity analysis excluding this study showed a similar effect, which is why we chose not to downgrade by another level.

[d]The certainty of evidence was downgraded by two levels due to the small numbers of participants.

BACKGROUND

Description of the condition

Anxiety is a human reaction to any unknown situation and is defined as a state of uneasiness and apprehension (Jellish 2012). Anxiety frequently occurs in patients throughout the perioperative period and has been described as the worst aspect of the perioperative experience (Jellish 2012; Johnston 1980; Walker 2016).

Preoperative anxiety is described as an unpleasant state of tension that occurs secondary to a patient being concerned about a disease, hospitalization, incapacitation, anaesthesia, or surgery, or his or her anticipation of postoperative pain and the unknown (Caumo 2001a; Ramsay 1972). In clinical studies, the prevalence of preoperative anxiety has varied widely, from 11% to 80%, depending on the methods used to assess it (Aust 2018; Corman 1958; Johnston 1980; Norris 1967; Wallace 1984). High levels of anxiety can occur for at least five or six days before admission to hospital; for some patients, anxiety remains high for several days after surgery (Johnston 1980). Risk factors for preoperative anxiety include female sex, high trait anxiety (tendency to experience anxiety), negative future perception, history of cancer and smoking, previous psychiatric disorder, moderate to intense depressive symptoms, and higher educational level (> 12 years) (Caumo 2001a). Previous surgery reduces the risk of preoperative anxiety (Caumo 2001a). Furthermore, preoperative anxiety has been found to correlate with high postoperative anxiety (Caumo 2001).

Historically, postoperative anxiety has received less attention than preoperative anxiety; however, recent evidence suggests that postoperative anxiety may have adverse effects on postoperative outcomes (Jellish 2012). Risk factors shown to be associated with postoperative anxiety are moderate to intense postoperative pain, preoperative state anxiety, history of smoking, negative future perception, and minor psychiatric disorder (Jellish 2012). Systemic multi-modal analgesia has been shown to be protective for postoperative anxiety (Jellish 2012).

According to the literature, medical interventions including the most widely used anxiolytic-sedatives (benzodiazepines), effective communication strategies in the perioperative period, cognitive-behavioural therapy (CBT), perioperative education, music therapy, massage therapy, and psychological preparation can be used successfully to reduce anxiety among surgical patients (Bailey 2010; Bradt 2013; Dao 2011; Jellish 2012, Kesanen 2017; Powell 2016; Wentworth 2009; Wilson 2016). Other drugs such as alpha- and beta-adrenoceptor blockers have been used to reduce preoperative anxiety, but they may result in cardiovascular complications (Blessberger 2019a; Blessberger 2019b; Duncan 2018). Other drugs (e.g. lidocaine (Weibel 2018; Weinstein 2018)) used to treat pain may also have calming or euphoric effects but usually are given postoperatively.

Description of the intervention

Melatonin (N-acetyl-5-methoxytryptamine) is synthesized from tryptophan and is secreted principally by the pineal gland. It has an endogenous circadian rhythm of secretion induced by the suprachiasmatic nuclei of the hypothalamus that is entrained to the light and dark cycle (Claustrat 2005). Melatonin has several putative functions including regulation of circadian rhythm, as well as sedative, analgesic, anxiolytic, anti-inflammatory, antioxidative, and oncostatic effects (Brzezinski 1997; Ebadi 1998; Maestroni 1993; Reiter 1995).

Exogenous melatonin is produced synthetically from reacting chemical compounds (Jarratt 2011). Synthetic melatonin is produced from pharmacy-grade ingredients under strict laboratory conditions in the form of tablets, capsules, liquids, or powder.

Although synthetic melatonin is molecularly identical to endogenous melatonin, its bioavailability varies widely (Harpsoe 2015). Oral doses (1 to 5 mg) result in serum melatonin concentrations that are 10 to 100 times higher than the usual night-time peak within one hour after ingestion, followed by a decline to baseline values in four to eight hours (Brzezinski 1997). Very low oral doses (0.1 to 0.3 mg) given in the daytime result in peak serum concentrations that are within the normal night-time range (Dollins 1994).

How the intervention might work

Anxiety is considered to be a multi-factorial phenomenon with genetic, biochemical, humoral, neurophysiological, and psychological factors (Nolte 2011).

Autoradiographic studies and receptor assays in humans have demonstrated the presence of melatonin receptors in various regions of the central nervous system (CNS) and other tissues (Stankov 1991). In addition, both experimental - Tian 2010 - and clinical studies - Acil 2004; Caumo 2007; Caumo 2009; Dianatkhah 2015; Ionescu 2008; Ismail 2009; Khare 2018; Khezri 2013; Khezri 2013b; Khezri 2016; Mowafi 2008; Naguib 1999; Naguib 2000; Naguib 2006; Norouzi 2019; Patel 2015; Torun 2019; Turkistani 2007 - have shown an anxiolytic effect of melatonin. Exogenous administration of melatonin has been found to facilitate the onset of sleep and to improve its quality (Wurtman 1995). As premedication, compared to widely used benzodiazepines, melatonin produces no residual effects or suppression of rapid eye movement sleep (Zhdanova 1995). Therefore, it could be a worthy alternative.

Due to various effects of melatonin (regulation of circadian rhythm, and sedative, analgesic, anti-inflammatory, antioxidative, and oncostatic effects (Brzezinski 1997; Ebadi 1998; Maestroni 1993; Reiter 1995)), it is not possible to distinguish the direct anxiolytic effect because it may occur as an interaction of several of these mechanisms.

Melatonin is considered a drug of low toxicity. A safety study done with very high oral doses of melatonin (50 mg/kg body weight orally) showed no serious adverse events (Nickkholgh 2011). In addition, a non-systematic review reported headache, dizziness, nausea, and sleepiness as the most common adverse effects (Andersen 2016). These review authors concluded that short-term use of melatonin is safe even in large doses. A systematic review assessed adverse effects of melatonin reported in 50 studies (Foley 2019). These review authors concluded that melatonin supplement in humans appears relatively safe, and that reported adverse events are generally minor, short-lived, and easily managed, with some exceptions in particular populations such as patients with Huntington's chorea.

Why it is important to do this review

Patients' preoperative anxiety influences their postoperative anxiety (Caumo 2001), pain (Bayrak 2019; Doleman 2018; Gorkem 2016; Kain 2000; Thomas 1995), analgesic requirements (Thomas 1995), length of hospital stay (Caumo 2001), and satisfaction with perioperative care and treatment (Ali 2017; Caumo 2001a; Jamison 1993). Perioperative anxiety can lead to aggressive reactions that result in an increase in distress experienced by the patient and can make management and control of postoperative pain more difficult (Caumo 2001a). In addition, psychological distress, including preoperative and postoperative anxiety, may lead to more frequent demands for analgesics in patient-controlled analgesia, as well as increased intraoperative analgesic requirements (Ip 2009; Pan 2006). Overall, it appears that patients with a high level of anxiety or a high level of distress preoperatively may experience higher rates of postoperative complications and may have impaired wound healing (Britteon 2017; Mavros 2011). Furthermore, preoperative anxiety has been shown to be a predictor of mortality and major morbidity in older patients (> 70 years) undergoing cardiac surgery (Williams 2013). Overall, treating anxiety in the perioperative period can improve the perioperative experience of the patient (Jellish 2012).

It is common practice in some day-case surgical units to use benzodiazepines, opioids, or beta-blockers as anxiolytic premedication when needed (Walker 2009). Their known adverse effects limit the safe use of these drugs. In particular, use of benzodiazepines can result in psychomotor impairment, cognitive impairment, daytime sleepiness, and sedation ('hang-over effect'), even after single-dose administration (Ashton 1994; Edwards 1981; Gudex 1991; Woods 1992).

Potential clinical benefits of new therapeutic options in this setting have been only sparsely investigated. Several studies have investigated the perioperative anxiolytic effects of melatonin (Capuzzo 2006; Dianatkhah 2015; Hoseini 2015; Pokharel 2014), and some have found positive results (Acil 2004; Caumo 2007; Caumo 2009; Ionescu 2008; Ismail 2009; Jain 2019; Khezri 2013; Khezri 2013b; Khezri 2016; Mowafi 2008; Naguib 1999; Naguib 2000; Naguib 2006; Norouzi 2019; Patel 2015; Torun 2019; Turkistani 2007). Furthermore, melatonin is a non-toxic drug with no reports of serious adverse events with short-term use (less than three months) (Andersen 2016; Buscemi 2006; Nordlund 1977; Seabra 2000).

The hypnotic, antinociceptive, and anticonvulsant properties of melatonin endow this neurohormone with the profile of a novel hypnotic-anaesthetic agent (Naguib 2007). Melatonin administration is also associated with a tendency towards faster recovery and a lower incidence of postoperative excitement than are seen with midazolam (Naguib 2007). Thus, we found it important and relevant to investigate whether melatonin can provide the preoperative and postoperative anxiolytic effects sometimes needed in day-case and in-patient surgery.

This is the first update of a previously published review (Hansen 2015). The purpose of updating this review was to explore if new trials have been published that would either alter or support the conclusions made in the previous review (Hansen 2015).

OBJECTIVES

To assess the effects of melatonin on preoperative and postoperative anxiety in adults compared to placebo or benzodiazepines.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized controlled- and cluster-randomized studies that were placebo-controlled or standard treatment-controlled, or both, that evaluated the effects of melatonin on preoperative or postoperative anxiety.

We included studies irrespective of language and publications status. We excluded quasi-randomized and cross-over studies.

Types of participants

We included adult patients of both sexes (15 to 90 years of age) undergoing any kind of surgical procedure for which it was necessary to use general, regional, or topical anaesthesia.

Types of interventions

To be included, patients had to receive melatonin, placebo, or a benzodiazepine administered on the day before surgery or immediately before surgery.

The intervention group (melatonin) was compared with a group receiving placebo or was compared with a group receiving benzodiazepines.

Types of outcome measures

Primary outcomes

Preoperative anxiety measured by a visual analogue scale (VAS), State-Trait Anxiety Inventory (STAI), or any other validated assessment tool. We regarded the preoperative period as the two hours leading up to either surgery or induction of anaesthesia. There were no restrictions regarding how long after premedication preoperative anxiety had to be assessed.

The STAI is a validated questionnaire used to assess anxiety. The scale is divided into two subscales: the Trait-Anxiety subscale consists of 20 questions focusing on a person's general level of fearfulness, whereas the State-Anxiety subscale measures immediate situational anxiety. The range of scores is 20 to 80 per subscale, with higher scores indicating greater anxiety. Trait-anxiety is a constant, whereas State-anxiety can differ according to the situation. The two subscales are not combined but are viewed separately.

VAS is a 100-mm scale, ranging from 0 to 100, whereby the extremes are marked "no anxiety" and "worst anxiety ever".

Both the simple VAS and the STAI have proved to be useful and valid measures of preoperative anxiety, and they are equivalent in terms of the assessment of preoperative anxiety (Kindler 2000; Millar 1995).

A minimal clinically important difference for preoperative and postoperative anxiety has not yet been fully established; however,

for acute pain assessment, a difference of 9 to 14 on a VAS has previously been estimated to be the minimal clinically significant difference (Kelly 1998; Kelly 2001). Therefore, we regarded a difference in preoperative and postoperative anxiety of 9 to 14 mm on a 0 to 100 mm VAS as clinically important.

To our knowledge, no minimal clinically important difference in STAI for preoperative and postoperative anxiety has been established. We viewed a difference of 10% (8 points on the STAI) as the minimal clinically important difference.

Secondary outcomes

Postoperative anxiety measured by VAS or STAI. Postoperative anxiety was divided into immediate postoperative anxiety (measured after surgery in the recovery room or at discharge from the recovery room) and delayed postoperative anxiety (measured six hours after surgery).

In addition, harms reported in the included studies were summarized qualitatively.

Search methods for identification of studies

This review is the first update of a previously published review (Hansen 2015). The search strategy has been updated to include additional search terms in the interest of improving the sensitivity of the search. Searches were conducted and reported as outlined in the *Cochrane Handbook for Systematic Review of Interventions* (Higgins 2019b). We did not impose any language or publication restrictions.

Electronic searches

We searched the following databases.

- Cochrane Central Register of Controlled Trials (CENTRAL; Issue 7 of 12; July 2020), in the Cochrane Library.
- MEDLINE ALL (Ovid SP, 1966 to July 2020).
- Embase (Ovid SP, 1980 to July 2020).
- Cumulative Index to Nursing and Allied Health Literature (CINAHL; EBSCOhost; 1982 to July 2020).
- Web of Science (SCI-EXPANDED 1945 to July 2020).

We searched CENTRAL using the terms found in Appendix 1. We adapted the search strategy for MEDLINE (Appendix 2), Embase (Appendix 3), CINAHL (Appendix 4), and Web of Science (Appendix 5). We combined the MEDLINE search with the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE (Lefebvre 2019). When appropriate, we used similar search strategies for identifying RCTs in the other databases. We searched the bibliographic references and citations of relevant studies and systematic reviews for further potentially relevant studies. We searched the following trial registries for unpublished and ongoing studies.

- ClinicalTrials.gov (https://www.clinicaltrials.gov/).
- World Health Organization International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/Default.aspx).

Searching other resources

We screened the reference lists of all eligible trials and reviews. The lead review author (BKM) contacted the authors of published trials to request additional information when necessary.

Data collection and analysis

Selection of studies

Using results of the above searches, we screened all titles and abstracts for eligibility and excluded the ones that clearly did not meet the inclusion criteria. Two review authors (BKM and DZ) independently performed this screening. For the remaining studies, we read the full manuscript or trial register entry to assess whether they should be included. If a trial was excluded, the reason for exclusion was documented (see Excluded studies).

In the case of insufficient published information to make a decision about inclusion, we contacted the corresponding author of the relevant trial (BKM). If a study was reported in a foreign language not understandable to the present review author group, a suitable translator was found.

Details on the included studies can be seen in the Characteristics of included studies tables.

Data extraction and management

One review author (BKM) independently extracted data twice using a standard form and looked for discrepancies before entering data into RevMan. Any discrepancies in the extracted data were resolved by discussion (BKM and DZ).

In the case of additional information being required, BKM contacted the corresponding author of the relevant trial. If a study was reported in a foreign language, a translator was found to help with extraction of data.

Data extracted included information on study design, country of origin, number of participants and demographic details, type of surgery and anaesthesia, intervention and dosing regimen, preoperative anxiety outcome measures, and postoperative anxiety outcome measures.

Assessment of risk of bias in included studies

One review author (BKM) independently assessed the methodological quality of the included trials. If a study was reported in a foreign language, we found a translator to assist with assessment of bias.

We performed the assessment as suggested in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* - Higgins 2011 - because we assessed risk of bias before the release of version 6.0 (Higgins 2019). See the 'Risk of bias' table in Characteristics of included studies.

Review authors assessed the risk of bias for the following domains.

- Random sequence generation.
- Allocation concealment.
- Incomplete outcome data.
- Selective reporting.
- Blinding of participants and personnel.

- Blinding of outcome assessment.
- Other potential sources of bias.

Review authors reviewed the aforementioned domains to perform an overall risk of bias assessment.

Review authors judged each of the above domains to have low (adequate), high (inadequate), or unclear risk of bias. If there were any doubts about the judgement, two review authors (BKM and DZ) resolved this uncertainty by discussion.

Random sequence generation (checking for possible selection bias)

We considered random sequence generation adequate if it was generated by a computer or by a random number table algorithm. We judged other processes - such as tossing a coin - to be adequate if the whole sequence was generated before the start of the trial, and if it was performed by a person not otherwise involved in patient recruitment.

We considered random sequence generation unclear if insufficient information was provided about the sequence generation process to permit judgement.

We considered random sequence generation inadequate if a non-random system, such as dates, names, or identification numbers, was used.

Allocation concealment (checking for possible selection bias)

We considered concealment adequate if the process used prevented patient recruiters, investigators, and participants from knowing the intervention allocation of the next participant to be enrolled in the study. Acceptable systems included a central allocation system, sealed opaque envelopes, or an on-site locked computer.

We considered allocation concealment unclear if the method of concealment was not described.

We considered concealment inadequate if the allocation method that was used allowed patient recruiters, investigators, or participants to know the treatment allocation of the next participant to be enrolled in the study. For example, alternate medical record numbers, reference to case record numbers or date of birth, an open allocation sequence, or unsealed envelopes.

Incomplete outcome data (checking for possible attrition bias)

We considered dropout or missing data reported as adequate if studies had no dropouts or missing data. We also considered the domain adequate if studies described reasons for dropouts, and if there were balanced numbers of participants dropping out across intervention groups.

Selective reporting (checking for possible reporting bias)

We considered selective reporting adequate if the study protocol was available, and if all of the study's pre-specified outcomes were reported in the article.

We considered selective reporting unclear if a study protocol was referred to but was not obtainable, or if no study protocol was available.

We considered selective reporting inadequate if one or more outcomes reported in the article were not pre-specified in the study protocol.

Blinding of participants and personnel (checking for possible performance bias)

We considered blinding adequate if participants and personnel were each blinded to the intervention. With regards to the intervention, we deemed blinding to be adequate if the melatonin, placebo, or benzodiazepines had an identical appearance.

We considered blinding unclear if there was insufficient information to permit judgement.

We considered blinding inadequate if participants and personnel were not blinded to the intervention.

Blinding of outcome assessment (checking for possible detection bias)

We considered blinding of outcome assessors adequate if the blinding was sufficiently described.

We considered blinding of outcome assessors unclear if there was insufficient information to permit judgement.

We considered blinding of outcome assessors inadequate if outcome assessors were not blinded.

Other potential biases

We considered other sources of bias not covered in the above domains.

Overall risk of bias

We assessed the domains blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting for each outcome. We performed an overall risk of bias assessment for each outcome, which we used to assess the certainty of evidence. Based on this assessment, we defined the included trials and each outcome result as showing low, unclear, or high risk of bias. An outcome was regarded to have low risk of bias if the included studies had an overall low risk of bias. If studies had low or unclear risk of bias in all domains, it was regarded as overall unclear risk of bias and if it was considered plausible that bias might raise some concerns about the results. If studies had high risk of bias for one or several domains, the overall risk of bias for the outcome was regarded as high, and it was interpreted that bias might seriously weaken confidence in the results.

Measures of treatment effect

We extracted VAS or STAI data for our primary outcome as the mean (standard deviation (SD)) or median (interquartile range (IQR) or range). We chose to analyse VAS or STAI data as continuous data and presented these as the mean difference (MD) when outcome measures were on the same scale. We expressed the overall results for our primary outcome as mean difference with 95% confidence intervals (CIs).

Unit of analysis issues

We included only randomized placebo-controlled, standard treatment-controlled, single- or double-blinded trials, and we excluded quasi-randomized and cross-over trials. We separated

comparisons (benzodiazepines vs melatonin and placebo vs melatonin) into two separate forest plots; hence there were no unit of analysis issues.

No cluster-randomised trials were found, but we had planned to include them in the meta-analysis. If such trials had been identified, we would have adjusted the sample size according to the method described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019), using an estimate of the intracluster correlation coefficient (ICC) derived from the trial or using external estimates obtained from similar studies or populations. Furthermore, a sensitivity analysis would be performed to investigate the robustness of conclusions.

Dealing with missing data

Whenever possible, we contacted the original investigators to request missing data.

We converted standard error of the mean (SEM) to standard deviation (SD), and we converted median (IQR or range) to mean (SD), using the methods outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019).

Assessment of heterogeneity

We assessed the clinical heterogeneity of included studies, assessed as clinical diversity (e.g. different types of anaesthesia (regional, general, topical), differences in patient characteristics, variable melatonin doses, differences in analgesics) and as methodological diversity (variability in study design and in risk of bias).

We assessed statistical heterogeneity with the I^2 statistic, thereby estimating the percentage of total variance across studies that was due to heterogeneity rather than to chance (Higgins 2019).

The authors interpreted values of the I^2 statistic as follows (Higgins 2019).

- 0% to 40%, might not be important.
- 30% to 60%, may represent moderate heterogeneity.
- 50% to 90%, may represent substantial heterogeneity.
- 75% to 100%, considerable heterogeneity.

Assessment of reporting biases

We assessed publication bias and small-study effects in a qualitative manner using a funnel plot in Review Manager 5.3 (RevMan 5.3). Because we had 27 included studies, we planned to look at whether the largest studies were near the average and small studies were spread on both sides of the average.

Data synthesis

We performed data synthesis and statistical analysis using Review Manager software (RevMan 5.3). Because the population was varied, we included all types of anaesthesia and surgery, adult participants of both sexes between the ages of 15 and 90 years, dosing regimens, and study sizes. Due to this variation, a random-effects model was deemed suitable for the meta-analysis.

As some studies used several different doses of melatonin or benzodiazepines, we chose to combine the groups receiving different doses of either melatonin or benzodiazepine into one melatonin or benzodiazepine group, respectively.

Studies reported our primary outcome as mean (SD) or median (IQR or range). For all studies reporting median, we assumed symmetrical distribution of data and used the median value directly in the meta-analyses as the mean. However, we decided to perform sensitivity analysis without studies reporting outcomes using a median (IQR), because the use of interquartile ranges rather than standard deviations can sometimes indicate that the outcome distribution is skewed (Higgins 2019). If the studies did not present data in a tabular fashion, we read the values directly from the graphs. If the studies reported changes from baseline (VAS change scores), we used corresponding negative or positive values. Both studies reporting VAS and those reporting VAS change scores were entered in the same meta-analysis as subgroups, and the results of both subgroups were pooled.

We converted SEM to SD using the method presented in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019). For all other studies, we converted median (IQR or range) to mean (SD) using the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019).

We analysed continuous data using an inverse variance method. We performed the analysis using Review Manager software (RevMan 5.3).

We chose to perform five meta-analyses.

- Primary outcome: melatonin versus placebo (VAS) preoperatively.
- Secondary outcome: melatonin versus placebo (VAS) postoperatively.
- Secondary outcome: melatonin versus placebo (STAI) postoperatively.
- Primary outcome: melatonin versus benzodiazepine (VAS) preoperatively.
- Secondary outcome: melatonin versus benzodiazepine (VAS) postoperatively.

Two studies measured preoperative anxiety using STAI, where one study used a modified version of STAI (STAI-S). Due to the limited number of studies, we chose not to perform meta-analysis on this primary outcome, and instead to provide a narrative description of study findings.

Subgroup analysis and investigation of heterogeneity

Studies that used VAS to measure anxiety reported the outcome either as VAS total or as change in VAS from baseline. We used a random-effects model when both subgroups (VAS total and change in VAS from baseline) were included in the same meta-analysis.

We performed three additional subgroup analyses to explore heterogeneity.

- Anaesthetic modality (regional or general).
- Participants' age (≤ 60 or > 60 years).
- Melatonin dose (anticipated range 1 to 20 mg).

We decided to divide studies into two groups according to the dose of melatonin administered (< 6 mg or ≥ 6 mg).

We explored if heterogeneity disappeared when the data were divided into subgroups depending on anaesthesia modality, participant age, or dose of melatonin administered.

Sensitivity analysis

We performed sensitivity analysis whereby we repeated the meta-analysis for preoperative anxiety (VAS) after excluding studies reporting only the median (IQR or range) for VAS data on preoperative anxiety. We did this because the use of interquartile ranges rather than standard deviations can sometimes be taken as an indicator that the outcome distribution is skewed (Higgins 2019).

We also performed sensitivity analysis for postoperative anxiety (VAS) after excluding studies reporting the median (IQR or range) for VAS data on postoperative anxiety, or studies reporting SD values of zero, which made us suspect that outcome was skewed.

We also performed a separate sensitivity analysis of our primary and secondary outcomes. We excluded all studies with an overall high risk of bias to be able to explore if studies with high risk of bias affected conclusions.

Summary of findings and assessment of the certainty of the evidence

We used the principles of the GRADE system (Guyatt 2008) to assess the certainty of the body of evidence associated with our primary outcome (preoperative anxiety) and secondary outcome (postoperative anxiety) and constructed "Summary of findings" (SoF) tables using Review Manager 5.3 (RevMan 5.3).

The GRADE approach appraises the certainty of a body of evidence-based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. The certainty of a body of evidence considers five domains: study limitations (risk of bias), inconsistent results, indirectness of evidence, imprecision, and publication bias. The certainty of evidence can be downgraded if a reason in the above-mentioned domains is found. If a serious reason was found the certainty of evidence was downgraded by one level if a very serious reason was found, the certainty of evidence was downgraded by two levels. We downgraded evidence if the outcome had an overall high risk of bias. However, if sensitivity analysis excluding studies with an overall high risk of bias showed a similar effect estimate, we decided not to downgrade evidence since we concluded that the inclusion of studies with a high risk of bias did not alter conclusions. We downgraded evidence if the outcome had high heterogeneity expressed with a high I^2 value. Evidence was downgraded if there were indirectness of evidence or high probability of publication bias. Also, evidence was downgraded if there were few participants and thus wide confidence intervals.

SoF tables were created for both intervention comparisons, including all primary and secondary outcomes:

- melatonin versus placebo: melatonin versus placebo (VAS) preoperatively, melatonin versus placebo (STAI) preoperatively, melatonin versus placebo (six-item STAI) preoperatively, melatonin versus placebo (VAS) immediate postoperative anxiety, melatonin versus placebo (STAI) delayed postoperative anxiety, melatonin versus placebo (six-item STAI) postoperatively
- melatonin versus benzodiazepine: melatonin versus benzodiazepine (VAS) preoperatively, melatonin versus benzodiazepine (STAI) preoperatively, melatonin versus benzodiazepine (six-item STAI) preoperatively, melatonin versus benzodiazepine (VAS) immediate postoperative anxiety, melatonin versus benzodiazepine (six-item STAI) postoperatively.

RESULTS

Description of studies

See Characteristics of included studies, Characteristics of excluded studies, Characteristics of studies awaiting classification, and Characteristics of ongoing studies.

Twenty-seven studies, published between 1999 and 2019, met the inclusion criteria.

Twenty-four studies compared melatonin with placebo. Twelve studies compared only melatonin with placebo (Abbasivash 2019; Capuzzo 2006; Caumo 2007; Ismail 2009; Jain 2019; Khezri 2013; Khezri 2016; Mowafi 2008; Naguib 2006; Norouzi 2019; Seet 2015; Turkistani 2007). In addition to placebo, six studies compared melatonin with the benzodiazepine midazolam (Acil 2004; Ionescu 2008; Naguib 1999; Naguib 2000; Patel 2015; Torun 2019), two compared melatonin with the benzodiazepine alprazolam (Khare 2018; Pokharel 2014), three compared melatonin with gabapentin (Hoseini 2015; Javaherforooshzadeh 2018; Khezri 2013b), and two compared melatonin with clonidine (Caumo 2009; Hoseini 2015). One study compared only melatonin with the benzodiazepine oxazepam (Dianatkhah 2015), and one compared melatonin with both pregabalin and alprazolam (Khanna 2019). Another study compared melatonin with gabapentin and placebo; however, the placebo group received 1 mg of midazolam intravenously during operation; hence, we decided to classify this study as having melatonin, gabapentin, and midazolam groups (Marzban 2016).

Results of the search

We identified 2881 references in primary electronic databases in July 2020 through our search strategy. We searched clinical trial registration databases and identified 1386 trial register records. We searched bibliographic references and citations of relevant studies and systematic reviews and identified two potential references.

Out of the total of 2881 database references, we removed 748 duplicates. In total, together with the 1386 records identified through other sources, we screened 3519 records and excluded 3424 records because they clearly did not meet the eligibility criteria (Figure 1).

Figure 1. Study flow diagram.

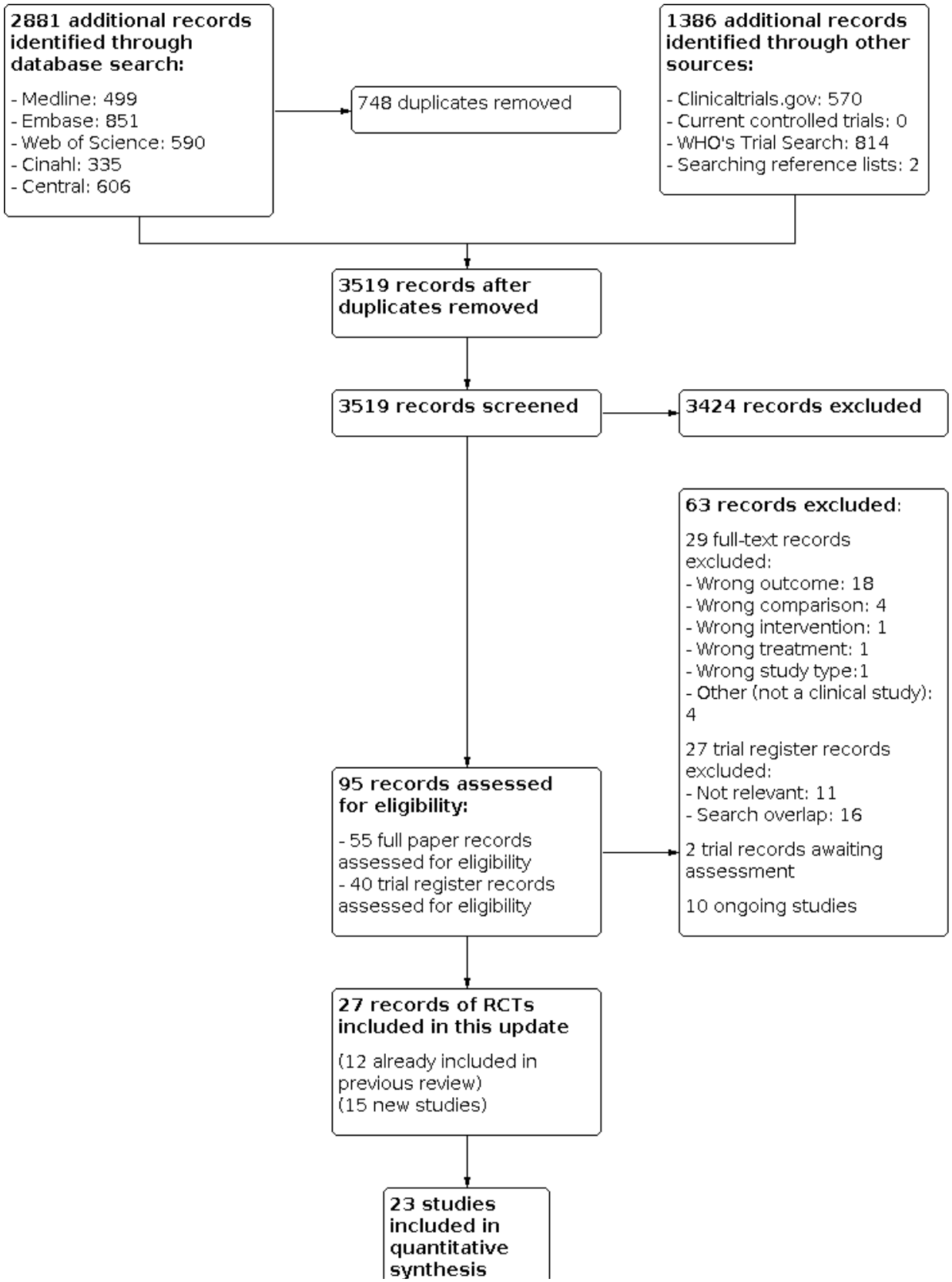
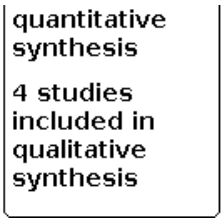


Figure 1. (Continued)



We conducted more in-depth screening of 95 records (including full-text reports and trial register records). We obtained full-text reports for 55 references found through our electronic database searches and through searching of reference lists, to check if they strictly fulfilled the inclusion criteria. We excluded 29 studies due to irrelevant interventions or outcomes, lack of an appropriate comparison group, or irrelevant study design, or because the report was a review article, PhD thesis summary, or conference abstract (Characteristics of excluded studies). In addition, we thoroughly read the full trial register records of 40 records found through our clinical trial registration database searches. Two studies were awaiting classification when we updated this review (Characteristics of studies awaiting classification). We retrieved the published manuscript for one study and therefore included it in our review (Marzban 2016). Furthermore, we found 10 ongoing studies (Characteristics of ongoing studies).

We found 27 studies that completely fulfilled the inclusion criteria for this review; 12 of these were included in the former review (Acil 2004; Capuzzo 2006; Caumo 2007; Caumo 2009; Ionescu 2008; Ismail 2009; Khezri 2013; Mowafi 2008; Naguib 1999; Naguib 2000; Naguib 2006; Turkistani 2007), and 15 were new additions (Abbasivash 2019; Dianatkhah 2015; Hoseini 2015; Jain 2019; Javaherforooshzadeh 2018; Khanna 2019; Khare 2018; Khezri 2013b; Khezri 2016; Marzban 2016; Norouzi 2019; Patel 2015; Pokharel 2014; Seet 2015; Torun 2019).

Included studies

See Characteristics of included studies for a description of the methods, participants, interventions, and outcomes of the individual studies.

A total of 2319 patients were randomized in the included studies, of whom 2227 patients (25 studies) had data concerning preoperative anxiety (Abbasivash 2019; Acil 2004; Capuzzo 2006; Dianatkhah 2015; Hoseini 2015; Ionescu 2008; Ismail 2009; Jain 2019; Javaherforooshzadeh 2018; Khanna 2019; Khare 2018; Khezri 2013; Khezri 2013b; Khezri 2016; Marzban 2016; Mowafi 2008; Naguib 1999; Naguib 2000; Naguib 2006; Norouzi 2019; Patel 2015; Pokharel 2014; Seet 2015; Torun 2019; Turkistani 2007), and 1354 patients (15 studies) had data concerning postoperative anxiety (Acil 2004; Capuzzo 2006; Caumo 2007; Caumo 2009; Dianatkhah 2015; Ionescu 2008; Javaherforooshzadeh 2018; Khanna 2019; Khezri 2013; Khezri 2013b; Khezri 2016; Marzban 2016; Naguib 1999; Naguib 2000; Norouzi 2019). The age of included patients ranged from 17 to 85 years. No cluster-randomized studies were found.

The number of participants in the included studies varied from 33 to 200. Of the 27 studies, five included only women (Caumo 2007; Caumo 2009; Naguib 1999; Naguib 2000; Khezri 2016), three included more females (Khare 2018; Pokharel 2014; Torun 2019), three included more men (Dianatkhah 2015; Khezri 2013b; Seet 2015), and 12 had a close to equal distribution of males and females (Abbasivash 2019; Capuzzo 2006; Ismail 2009; Jain 2019; Javaherforooshzadeh 2018; Khezri 2013; Marzban 2016; Mowafi 2008; Naguib 2006; Norouzi 2019; Patel 2015; Turkistani 2007), with the exception of two studies that had a greater number of females in the placebo group - Naguib 2006 - and in the midazolam group - Patel 2015 - respectively. Three studies did not provide information on distribution of sex (Acil 2004; Hoseini 2015; Khanna 2019), and the remaining study did not define which group was female or male (Ionescu 2008). Seventeen of the 27 studies were carried out in Middle East countries (Saudi Arabia, Turkey, and Iran), one in Italy, one in Romania, two in Brazil, four in India, one in Singapore, and one in Nepal.

Three studies used STAI to measure anxiety (Caumo 2007; Caumo 2009; Hoseini 2015), one used a modified version of STAI (STAI-S) consisting of six items from the STAI questionnaire producing a total score between 6 to 24 (Ionescu 2008), one used the Hamilton Anxiety Rating Scale (HAM-A) (Dianatkhah 2015), one used a numerical rating scale (NRS) (Capuzzo 2006), one used the Beck Anxiety Inventory (BAI) (Khanna 2019), and the remaining studies assessed anxiety using a visual or verbal anxiety scale (VAS) (Abbasivash 2019; Acil 2004; Ismail 2009; Jain 2019; Javaherforooshzadeh 2018; Khare 2018; Khezri 2013; Khezri 2013b; Khezri 2016; Marzban 2016; Mowafi 2008; Naguib 1999; Naguib 2000; Naguib 2006; Norouzi 2019; Patel 2015; Pokharel 2014; Seet 2015; Torun 2019; Turkistani 2007).

Twenty-two studies compared melatonin with placebo for preoperative anxiety (Abbasivash 2019; Acil 2004; Capuzzo 2006; Hoseini 2015; Ionescu 2008; Ismail 2009; Jain 2019; Javaherforooshzadeh 2018; Khare 2018; Khezri 2013; Khezri 2013b; Khezri 2016; Mowafi 2008; Naguib 1999; Naguib 2000; Naguib 2006; Norouzi 2019; Patel 2015; Pokharel 2014; Seet 2015; Torun 2019; Turkistani 2007). Eighteen studies used a VAS to measure anxiety (Acil 2004; Ismail 2009; Jain 2019; Javaherforooshzadeh 2018; Khare 2018; Khezri 2013; Khezri 2013b; Khezri 2016; Mowafi 2008; Naguib 1999; Naguib 2000; Naguib 2006; Norouzi 2019; Patel 2015; Pokharel 2014; Seet 2015; Torun 2019; Turkistani 2007), and two studies used STAI and a six-item STAI, respectively (Hoseini 2015; Ionescu 2008). Because these two studies were not comparable to the rest, we decided not to include these two studies in the meta-analysis. One study used an NRS (Capuzzo 2006), and we assumed that this was comparable to the VAS (Hjermstad 2011).

Eleven studies compared melatonin with placebo in the recovery room, in the recovery room at discharge, or 90 minutes postoperatively (Acil 2004; Capuzzo 2006; Ionescu 2008; Javaherforooshzadeh 2018; Khezri 2013; Khezri 2013b; Khezri 2016; Marzban 2016; Naguib 1999; Naguib 2000; Norouzi 2019). Of these, 10 studies used VAS or NRS to measure anxiety (Acil 2004; Capuzzo 2006; Javaherforooshzadeh 2018; Khezri 2013; Khezri 2013b; Khezri

2016; Marzban 2016; Naguib 1999; Naguib 2000; Norouzi 2019), whereas one study used a six-item STAI and therefore was not included in the meta-analysis (Ionescu 2008).

Four studies compared melatonin with placebo six hours postoperatively (Caumo 2007; Caumo 2009; Javaherforooshzadeh 2018; Ionescu 2008). Three studies measured postoperative anxiety using the STAI (Caumo 2007; Caumo 2009; Ionescu 2008); however, Ionescu 2008 used a six-item state anxiety scale (STAI-S) and therefore was not included in the meta-analysis. One study measured postoperative anxiety using a VAS (Javaherforooshzadeh 2018). This study was not included in the meta-analysis for six hours postoperative because it was not comparable with the remaining two studies, which measured delayed postoperative anxiety using the STAI (Caumo 2007; Caumo 2009).

Eleven studies compared melatonin with a benzodiazepine for preoperative anxiety (Acil 2004; Dianatkhah 2015; Ionescu 2008; Khanna 2019; Khare 2018; Marzban 2016; Naguib 1999; Naguib 2000; Patel 2015; Pokharel 2014; Torun 2019). Eight studies used a VAS to measure anxiety (Acil 2004; Khare 2018; Marzban 2016; Naguib 1999; Naguib 2000; Patel 2015; Pokharel 2014; Torun 2019), one study used a six-item STAI (Ionescu 2008), one study used HAM-A (Dianatkhah 2015), and one study used BAI (Khanna 2019). Dianatkhah 2015 Ionescu 2008, and Khanna 2019 were not included in the meta-analysis because the scales used were not comparable to the visual or verbal anxiety scale.

Seven studies compared melatonin with a benzodiazepine 60 to 90 minutes postoperatively (Acil 2004; Dianatkhah 2015; Ionescu 2008; Khanna 2019; Marzban 2016; Naguib 1999; Naguib 2000). Four studies used a VAS to measure anxiety (Acil 2004; Marzban 2016 Naguib 1999; Naguib 2000). One study used the HAM-A (Dianatkhah 2015), one study used the BAI (Khanna 2019), and one study used the six-item STAI (Ionescu 2008); these studies were not included in the meta-analysis.

For eight studies (Acil 2004; Caumo 2007; Caumo 2009; Ismail 2009; Khezri 2016; Naguib 1999; Naguib 2000; Pokharel 2014), data were presented only graphically. For one study (Naguib 2000), the graph for melatonin and midazolam was difficult to read, and study authors were contacted, but we received no answer. From the graph, the mean and the SD had to be measured with a ruler to interpret the VAS score. In Naguib 1999, it was straightforward to measure mean and SD for both placebo and melatonin arms. In Naguib 2000, the mean of the placebo arm could be read, and we assumed that the bar with the highest value indicated the SD of the placebo group. For melatonin and midazolam arms, three doses were used, and the means of doses were pooled, as they had equal numbers of participants. We did not find it possible to read the SD of the six arms, as we could not distinguish the error bars. Therefore, we chose to impute the SD for both melatonin and midazolam arms from the SD of the placebo arm. For Khezri 2016, it is not clear if the graph presented the outcome as mean (SD) or median (IQR or range). In the methods section of the manuscript, the author of the study stated that normally distributed data would be presented as mean (SD). Still, we were not able to verify if the data were normally distributed. Khezri 2016 also measured anxiety on a scale from 0 to 10 and graphically illustrated a scale going from 0 to 18. Therefore, we chose not to include the study in our meta-analysis, because we could not with certainty conclude what the graph showed (we contacted the study author by email but received no reply). Acil 2004 did not report an SD for preoperative or postoperative anxiety (we contacted the study author but received no answer), so we did not include this study in the meta-analysis as the conversion from P value to SD was not possible. Khanna 2019, using the BAI, also provided no SD values or range. Study authors provided no contact information, so we were unable to contact them.

One study did not report how outcomes were presented (Marzban 2016), but we assumed they were presented as mean SD (the study author was contacted by email and confirmed this). The study compared melatonin to a placebo. However, the placebo group was given midazolam before preoperative anxiety was measured; therefore, we chose to consider the placebo group as a midazolam group and included the study in the meta-analysis comparing melatonin to a benzodiazepine. The study reported SD values of 0, indicating that distribution was skewed, and melatonin and the comparator (midazolam) were given at different times via different administration routes. Therefore, we decided not to include this study in the sensitivity analysis.

Eight studies reported preoperative anxiety as median (range or IQR) (Capuzzo 2006; Ismail 2009; Khezri 2013; Khezri 2013b; Mowafi 2008; Naguib 2006; Pokharel 2014; Turkistani 2007), and two studies reported postoperative anxiety as mean (SEM) (Caumo 2007; Caumo 2009). We converted these to mean (SD) using the method provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019). However, because this method was not robust, we performed sensitivity analysis on preoperative anxiety while excluding the eight studies (Capuzzo 2006; Ismail 2009; Khezri 2013; Khezri 2013b; Mowafi 2008; Naguib 2006; Pokharel 2014; Turkistani 2007). Three additional studies reported medians of zero (Capuzzo 2006; Khezri 2013; Khezri 2013b), thereby violating the assumption of symmetry; they were not included in the sensitivity analysis.

We decided to perform an additional sensitivity analysis whereby we excluded all studies with overall high risk of bias from our meta-analysis. Eight studies were assessed as having overall high risk of bias, and of these, we excluded seven studies from the sensitivity analysis (Hoseini 2015; Javaherforooshzadeh 2018; Khezri 2013; Khezri 2013b; Marzban 2016; Norouzi 2019; Pokharel 2014). The remaining study was not included in any meta-analysis (Dianatkhah 2015).

Type of surgery and anaesthesia

Two studies were performed in patients undergoing abdominal hysterectomy (Caumo 2007; Caumo 2009), four studies in patients undergoing cataract surgery (Ismail 2009; Khezri 2013; Khezri 2013b; Marzban 2016), four studies in patients undergoing laparoscopic cholecystectomy (Acil 2004; Ionescu 2008; Pokharel 2014; Hoseini 2015), two studies in patients undergoing gynaecological laparoscopic procedures (Naguib 1999; Naguib 2000), one study in patients undergoing caesarean section (Khezri 2016), two studies in patients undergoing elective hand surgery (Abbasivash 2019; Mowafi 2008), five studies in patients undergoing different surgical procedures (not specified) (Capuzzo 2006; Jain 2019; Khare 2018; Patel 2015; Turkistani 2007), one study in patients undergoing laparoscopic surgery (Khanna 2019), one study in patients having coronary artery bypass surgery (CABG) (Dianatkhah 2015), one study in patients having spinal surgery at two or three levels of laminectomy (Javaherforooshzadeh 2018), one study in patients undergoing elective extraction of all four wisdom teeth (Seet 2015), one study in patients undergoing impacted mandibular

third molar surgery (Torun 2019), one study in patients undergoing non-emergency abdominal surgery (Norouzi 2019), and one study in which researchers did not specify the type of surgery performed (Naguib 2006).

Seventeen studies used general anaesthesia (Acil 2004; Caumo 2007; Caumo 2009; Hoseini 2015; Ionescu 2008; Jain 2019; Javaherforooshzadeh 2018; Khanna 2019; Khare 2018; Naguib 1999; Naguib 2000; Naguib 2006; Norouzi 2019; Patel 2015; Pokharel 2014; Seet 2015; Turkistani 2007), four used topical anaesthesia (Ismail 2009; Khezri 2013; Khezri 2013b; Marzban 2016), three used regional or local anaesthesia (Abbasivash 2019; Mowafi 2008; Torun 2019), one used spinal anaesthesia (Khezri 2016), and one did not specify the type of anaesthesia given (Dianatkhah 2015). One study used both general and spinal anaesthesia (Capuzzo 2006).

Interventions

Melatonin doses varied from 3 mg to 10 mg in the majority of studies. However, four studies administered melatonin as mg/kg ranging from 0.05 to 0.4 mg/kg (Naguib 2000; Naguib 2006; Patel 2015; Torun 2019). Seventeen studies administered melatonin orally (Abbasivash 2019; Capuzzo 2006; Caumo 2007; Caumo 2009; Hoseini 2015; Ismail 2009; Jain 2019; Javaherforooshzadeh 2018; Khanna 2019; Khare 2018; Marzban 2016; Mowafi 2008; Patel 2015; Pokharel 2014; Seet 2015; Torun 2019; Turkistani 2007), nine studies administered melatonin sublingually (Acil 2004; Ionescu 2008; Khezri 2013; Khezri 2013b; Khezri 2016; Naguib 1999; Naguib 2000; Naguib 2006; Norouzi 2019), and one study did not describe the administration route (Dianatkhah 2015).

Melatonin was administered approximately 20 to 120 minutes before either surgery or induction of anaesthesia. Three studies also administered one dose of melatonin the evening before surgery (Caumo 2007; Caumo 2009; Ionescu 2008). One study administered only melatonin one hour before assigned sleep time the night before surgery (Dianatkhah 2015), and one study administered melatonin on the day of surgery but did not provide more detail (Capuzzo 2006).

Midazolam was administered in doses ranging from 1 to 15 mg or from 0.05 to 0.2 mg/kg. Alprazolam was administered in doses ranging from 0.25 to 0.5 mg. One study compared melatonin to 10 mg oxazepam (Dianatkhah 2015). Some studies also compared melatonin to clonidine or gabapentin (Caumo 2009; Hoseini 2015; Javaherforooshzadeh 2018; Khezri 2013b; Marzban 2016). Clonidine was administered in doses of 0.1 to 0.2 mg, and the gabapentin dose was 600 mg in all studies. One study also compared melatonin to 75 mg pregabalin (Khanna 2019)

Adverse effects

See Table 1 for more information on adverse effects described in primary study reports.

Fourteen studies did not report on adverse effects (Abbasivash 2019; Acil 2004; Capuzzo 2006; Caumo 2007; Caumo 2009; Dianatkhah 2015; Hoseini 2015; Khare 2018; Marzban 2016; Naguib 2006; Norouzi 2019; Patel 2015; Seet 2015; Turkistani 2007). However, six of these studies examined psychomotor and cognitive function (Acil 2004; Dianatkhah 2015; Khare 2018; Naguib 2006; Norouzi 2019; Patel 2015). Three studies found that benzodiazepines impaired psychomotor and cognitive function compared with melatonin and placebo (Acil 2004; Khare 2018; Patel 2015). Dianatkhah 2015 examined incidences of delirium and found that a smaller proportion experienced delirium in the melatonin group compared with the oxazepam group; however, this difference was not statistically relevant. Norouzi 2019 found that orientation was impaired in the melatonin group compared with the placebo group for one preoperative event, and Naguib 2006 found no difference in orientation scores between melatonin and placebo groups. Seven studies evaluated sedation (Acil 2004; Khare 2018; Marzban 2016; Naguib 2006; Norouzi 2019; Patel 2015; Seet 2015). Three studies found that benzodiazepines produced the highest degree of sedation but melatonin also showed sedative properties (Acil 2004; Khare 2018; Patel 2015). Three studies found no difference in sedation between melatonin and placebo (Naguib 2006; Norouzi 2019; Seet 2015). The remaining study found that melatonin and midazolam produced a higher degree of sedation compared with gabapentin (Marzban 2016). One study explored the severity of nausea and vomiting and found no differences between melatonin, gabapentin, clonidine, and placebo groups (Hoseini 2015). One study reported that mean arterial pressure (MAP) was lower in the melatonin group at all times compared with the placebo group (Norouzi 2019).

Six studies specifically reported that no side effects were observed (Ionescu 2008; Jain 2019; Javaherforooshzadeh 2018; Naguib 1999; Naguib 2000; Torun 2019). However, four of these studies assessed psychomotor and cognitive function as well as sedation (Ionescu 2008; Naguib 1999; Naguib 2000; Torun 2019). Two studies reported amnesia in the benzodiazepine groups (Ionescu 2008; Naguib 1999), three studies found that benzodiazepines impaired psychomotor and cognitive function (Naguib 1999; Naguib 2000; Torun 2019); one of these studies also found that melatonin caused impairment on the Digit-Symbol Substitution Test (DSST) postoperatively (Naguib 1999), and one study found that DSST scores were lower in the melatonin group compared with the placebo group after administration of medication (Torun 2019). The remaining study found no difference in orientation score (Naguib 2000). Four studies reported that benzodiazepines caused the highest sedation score compared with melatonin and placebo (Ionescu 2008; Naguib 1999; Naguib 2000; Torun 2019); however, melatonin also showed sedative properties.

The remaining seven studies reported adverse effects (Ismail 2009; Khanna 2019; Khezri 2013; Khezri 2013b; Khezri 2016; Mowafi 2008; Pokharel 2014). Cases of headache in the melatonin group were described in three studies (Khezri 2013; Khezri 2013b; Khezri 2016), a case of dizziness in the melatonin group was described in one study (Ismail 2009), and one study described two cases of excessive sleepiness in the melatonin group (Mowafi 2008). One study reported that no difference in occurrence of vomiting, headache, dizziness, and restlessness was seen between groups (Pokharel 2014). Another study reported that side effects, such as headache and dizziness, were similar in melatonin, pregabalin, and alprazolam groups (Khanna 2019). Two studies reported a decrease in MAP after melatonin administration (Ismail 2009; Mowafi 2008). Three studies viewed sedation, and one of these studies found that gabapentin increased sedation (Khezri 2013b), one study found that combination drugs of alprazolam and placebo or alprazolam and melatonin increased levels of sedation (Pokharel 2014), and one study found that melatonin produced the highest degree of sedation compared with alprazolam and pregabalin (Khanna 2019).

Missing information and unspecified issues

In the case of any missing information or unspecified issues, we contacted the study authors to clarify these issues. Details are available in the "notes" in the Characteristics of included studies section. Khanna 2019, however, provided no contact information, and we were unable to contact these authors to clarify unspecified issues.

One study was written in Farsi (Marzban 2016), and we contacted a suitable translator to help with extracting data and assessing bias.

Excluded studies

We excluded 36 studies; for detailed reasons, see Characteristics of excluded studies.

Awaiting classification

Two studies are awaiting classification (IRCT20160430027677N8; CTRI/2017/08/009245); see Characteristics of studies awaiting classification.

Ongoing studies

Ten studies are ongoing (CTRI/2018/02/011895; CTRI/2018/04/012960; CTRI/2018/08/015192; CTRI/2018/08/015537; CTRI/2018/10/015917; CTRI/2019/12/022358; CTRI/2020/02/023330; IRCT20100707004345N6; IRCT20190120042432N1; NCT02386319); see Characteristics of ongoing studies.

Risk of bias in included studies

We assessed each study using the Cochrane risk of bias tool presented in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Overall findings are presented in the 'Risk of bias' graph (Figure 2), which shows the review authors' judgements about each risk of bias item presented as percentages across all included studies; and in the 'Risk of bias' summary (Figure 3), which shows the review authors' judgements about each risk of bias item for each included study. We produced an overall risk of bias judgement for each outcome and for each study.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

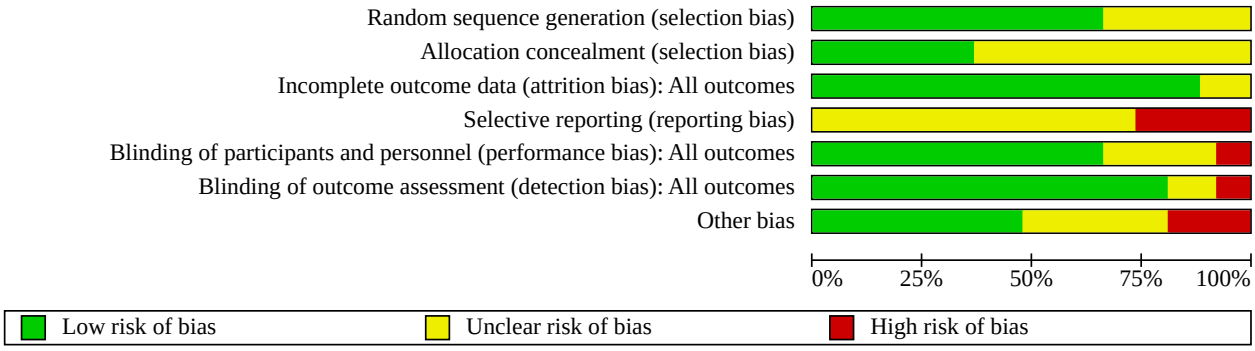


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

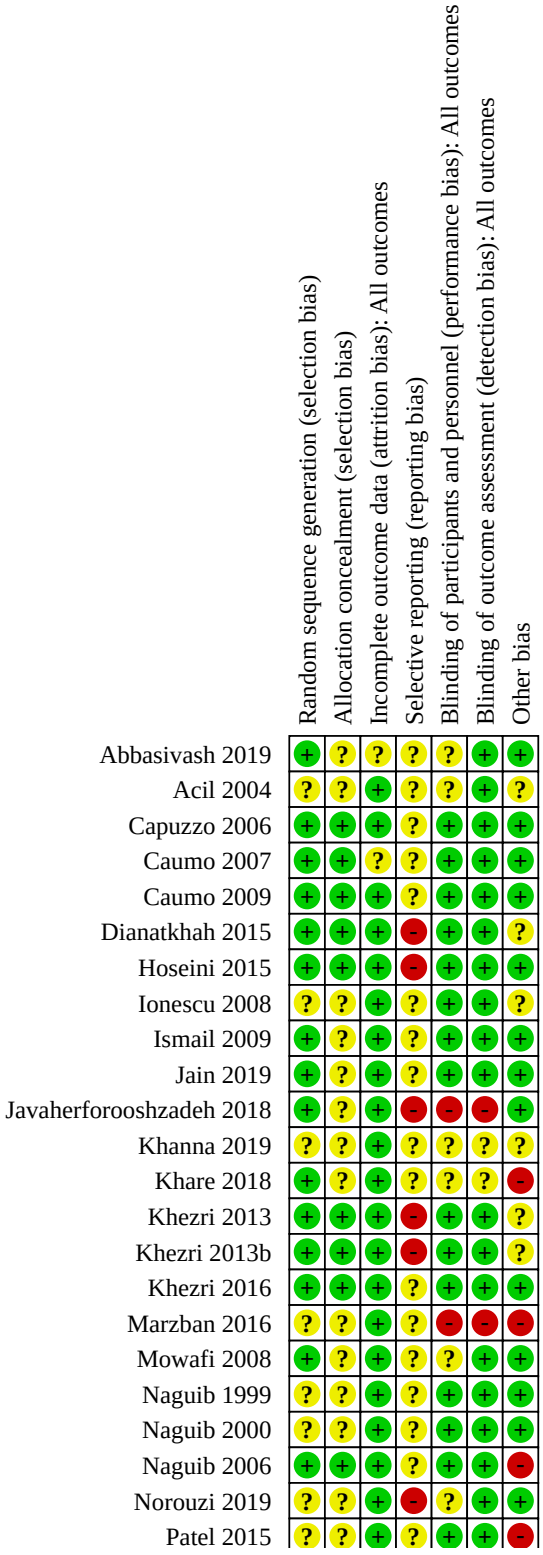
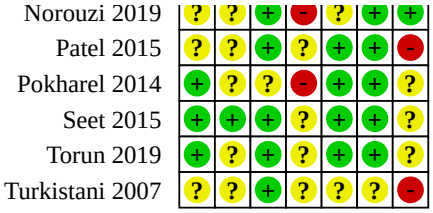


Figure 3. (Continued)



Allocation

Ten studies adequately described the method used to generate the random sequence and conceal the allocation (Capuzzo 2006; Caumo 2007; Caumo 2009; Dianatkhah 2015; Hoseini 2015; Khezri 2013; Khezri 2013b; Khezri 2016; Naguib 2006; Seet 2015), whereas eight studies did not describe it adequately (Acil 2004; Ionescu 2008; Marzban 2016; Naguib 1999; Naguib 2000; Norouzi 2019; Patel 2015; Turkistani 2007). Eight studies described the method used to generate the random sequence adequately but did not describe how the allocation was concealed sufficiently (Abbasivash 2019; Ismail 2009; Jain 2019; Javaherforooshzadeh 2018; Khare 2018; Mowafi 2008; Pokharel 2014; Torun 2019). One study provided no information regarding randomization or allocation concealment (Khanna 2019). No studies had high risk of selection bias .

Blinding

Blinding of participants and personnel was adequately described in 18 studies (Capuzzo 2006; Caumo 2007; Caumo 2009; Dianatkhah 2015; Hoseini 2015; Ionescu 2008; Ismail 2009; Jain 2019; Khezri 2013; Khezri 2013b; Khezri 2016; Naguib 1999; Naguib 2000; Naguib 2006; Patel 2015; Pokharel 2014; Seet 2015; Torun 2019), and 21 studies adequately described blinding of outcome assessors (Abbasivash 2019; Acil 2004; Capuzzo 2006; Caumo 2007; Caumo 2009; Dianatkhah 2015; Hoseini 2015; Ionescu 2008; Ismail 2009; Khezri 2013; Khezri 2013b; Khezri 2016; Mowafi 2008; Naguib 1999; Naguib 2000; Naguib 2006; Norouzi 2019; Patel 2015; Pokharel 2014; Seet 2015; Torun 2019). Two studies had high risk of bias in both blinding of participants and personnel and blinding of outcome assessors (Javaherforooshzadeh 2018; Marzban 2016). Seven studies had unclear risk of performance bias (Abbasivash 2019; Acil 2004; Khanna 2019; Khare 2018; Mowafi 2008; Norouzi 2019; Turkistani 2007), and three studies had unclear risk of detection bias (Khanna 2019; Khare 2018; Turkistani 2007).

Incomplete outcome data

All studies included in this review, except two (Caumo 2007; Pokharel 2014), had low risk of attrition bias. Studies adequately accounted for their dropouts and reported reasons for attrition and exclusion.

Selective reporting

We noted unclear risk of reporting bias as no study protocol was available for 19 studies. Seven studies were assessed as having high risk of bias because protocols were not consistent with what was reported in the articles (Dianatkhah 2015; Hoseini 2015; Javaherforooshzadeh 2018; Khezri 2013; Khezri 2013b; Norouzi 2019; Pokharel 2014).

Other potential sources of bias

None of the studies reported receipt of funding from drug manufacturers or agencies with commercial interests. Eleven studies reported funding or grants received from academic, institutional, or departmental sources; however, this was not seen as a basis for bias.

Thirteen studies had low risk of bias for this domain (Abbasivash 2019; Capuzzo 2006; Caumo 2007; Caumo 2009; Hoseini 2015; Ismail 2009; Jain 2019; Javaherforooshzadeh 2018; Khezri 2016; Mowafi 2008; Naguib 1999; Naguib 2000; Norouzi 2019). Eight studies had unclear risk of bias because of an uneven distribution of sex; however, this uneven distribution was similar in all treatment groups, or there was no mention of sex distribution (Acil 2004; Dianatkhah 2015; Ionescu 2008; Khanna 2019; Khezri 2013b; Pokharel 2014; Seet 2015; Torun 2019). The remaining six studies had high risk of bias based on an uneven distribution of females and males in some treatment groups, an uneven distribution of age, or both (Khare 2018; Khezri 2013; Marzban 2016; Naguib 2006; Patel 2015; Turkistani 2007).

Summary assessments of risk of bias

No study had low risk of bias for all domains (allocation, blinding, incomplete outcome data, selective reporting). Most studies had unclear risk of bias for one or more domains and were regarded as having overall unclear risk of bias (Abbasivash 2019; Acil 2004; Capuzzo 2006; Caumo 2007; Caumo 2009; Ionescu 2008; Ismail 2009; Jain 2019; Khanna 2019; Khare 2018; Khezri 2016; Mowafi 2008; Naguib 1999; Naguib 2000; Naguib 2006; Patel 2015; Seet 2015; Torun 2019; Turkistani 2007). Eight studies had high risk of bias in one or more domains, and the overall bias assessment for these studies was that they were at high risk of bias (Dianatkhah 2015; Hoseini 2015; Javaherforooshzadeh 2018; Khezri 2013; Khezri 2013b; Marzban 2016; Norouzi 2019; Pokharel 2014). We did not regard "other sources of bias" as a key domain; therefore, we did not include this domain in our overall risk of bias assessments.

Our overall risk of bias assessment for our primary and secondary outcomes can be seen in the summary of findings tables (Summary of findings 1; Summary of findings 2). We performed sensitivity analysis while excluding all studies with overall high risk of bias to assess if inclusion of these studies would alter our conclusions (Table 2).

Effects of interventions

See: **Summary of findings 1** Summary of findings; **Summary of findings 2** Summary of findings

See "Summary of findings" tables (Summary of findings 1; Summary of findings 2), "Additional" tables (Table 2; Table 3; Table 4; Table 5), and "Data and analyses" tables (Data and analyses).

We assessed preoperative anxiety between 20 and 120 minutes after premedication to enable data extraction from all studies. If studies applied different doses of melatonin or benzodiazepines, we pooled the reported results.

We did not include Acil 2004 in meta-analysis because no standard deviation (SD) was reported, and we did not include Khezri 2016 in meta-analysis because we were unable to extract data from the graph presented in the study.

In total, we excluded nine studies from sensitivity analysis (Capuzzo 2006; Ismail 2009; Khezri 2013; Khezri 2013b; Marzban 2016; Mowafi 2008; Naguib 2006; Pokharel 2014; Turkistani 2007). We made these exclusions either because these studies reported only median (interquartile range (IQR) or range) for visual analogue scale (VAS) data on preoperative anxiety (we contacted the corresponding author of these studies to retrieve more detailed data, but we received no response or we encountered email delivery failure) or, in the case of one study (Marzban 2016), because benzodiazepine and melatonin were distributed at different times, and we, therefore, suspected that the study was not sufficiently blinded.

We assessed postoperative anxiety at two different time points. We chose to group results obtained while in the recovery room, at recovery room discharge, and 90 minutes postoperatively as one group, and six hours postoperatively as another, to explore immediate and delayed anxiety, respectively.

We did not include Acil 2004 in meta-analysis because no SD was reported, and we did not include two other studies in meta-analysis because they used the Beck Anxiety Inventory (BAI) and a modified version of State-Trait Anxiety Inventory (STAI-S) (Ionescu 2008; Khanna 2019), respectively, which were not comparable to the VAS. We performed sensitivity analysis after exclusion of three studies (Capuzzo 2006; Khezri 2013; Marzban 2016). We excluded these because they reported medians of zero, thereby violating the assumption of symmetry.

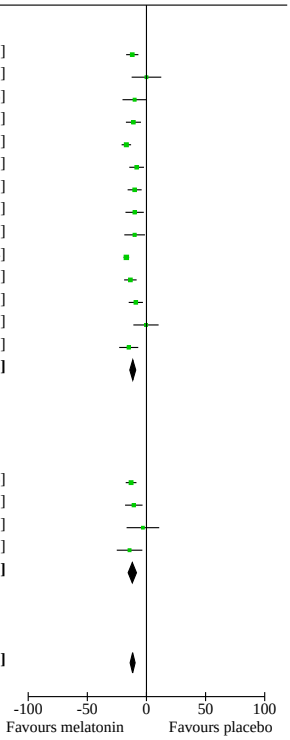
Melatonin versus placebo

Preoperative anxiety

The meta-analysis comparing melatonin with placebo showed a reduction in preoperative anxiety measured by a VAS (mean difference (MD) -11.69, 95% confidence interval (CI) -13.80 to -9.59; P < 0.00001, I^2 = 49%; 18 studies, 1264 participants; moderate-certainty evidence; Analysis 1.1; Figure 4). The 95% CI is relatively narrow, making us certain that melatonin reduces preoperative anxiety compared with placebo. When performing a sensitivity analysis of only studies that reported the outcome using the mean (SD), we showed a reduction in preoperative anxiety (MD -11.90, 95% CI -14.24 to -9.55; P < 0.00001, I^2 = 34%; 10 studies, 671 participants; Table 4).

Figure 4. Forest plot of comparison: 1 Melatonin versus placebo, outcome: 1.1 Preoperative anxiety (VAS) (mm) with subgroup 1.1.1 Final VAS scores and subgroup 1.1.2 Change VAS scores.

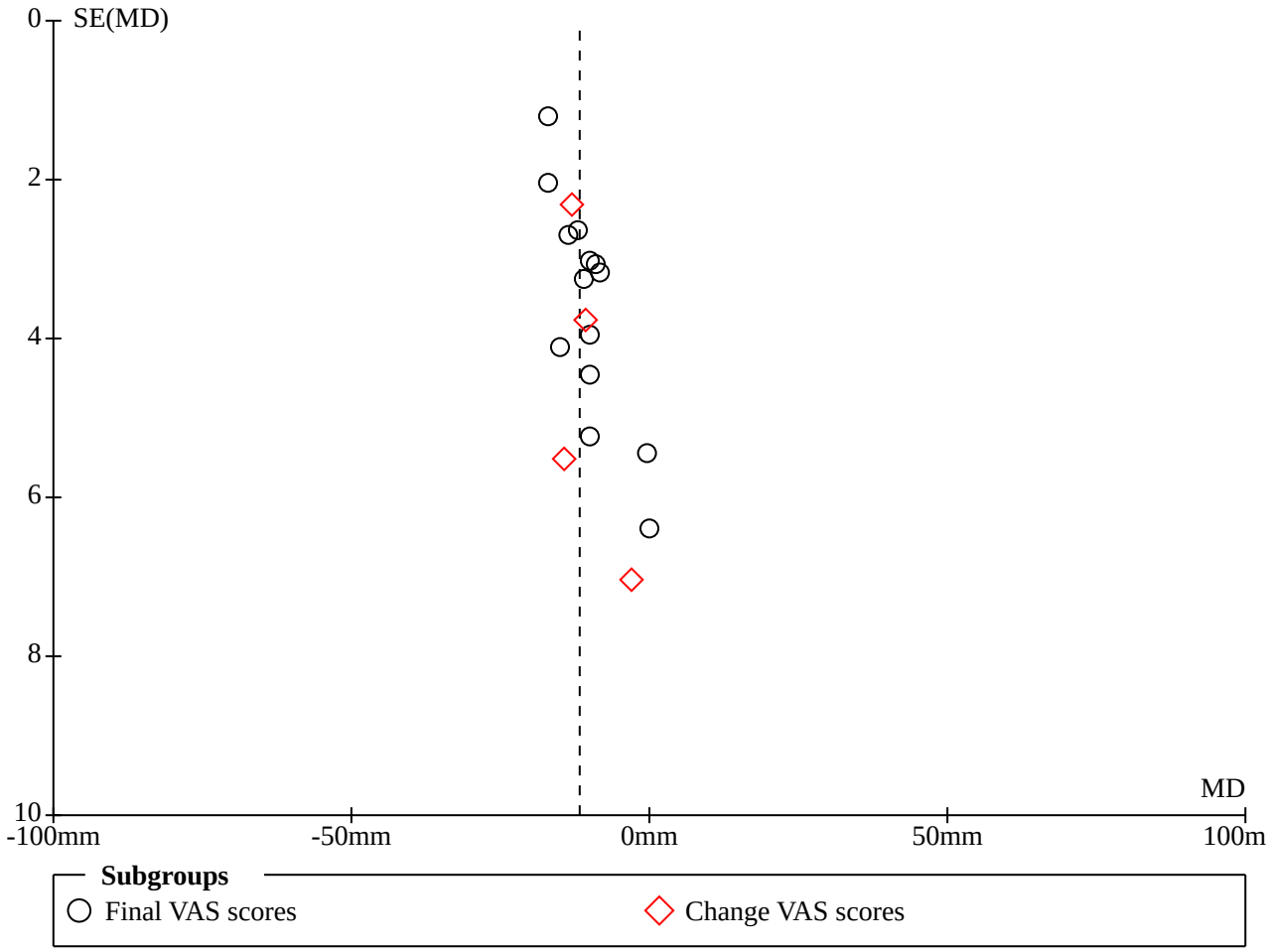
Study or Subgroup	Melatonin Mean [mm]	Melatonin SD [mm]	Melatonin Total	Placebo Mean [mm]	Placebo SD [mm]	Placebo Total	Weight	Mean Difference IV, Random, 95% CI [mm]
1.1.1 Final VAS scores								
Abbasivash 2019	30	8.1	25	42	10.4	25	7.4%	-12.00 [-17.17 , -6.83]
Capuzzo 2006	30	29.6	67	30	44.4	71	2.3%	0.00 [-12.53 , 12.53]
Ismail 2009	30	7.4	20	40	22.2	20	3.2%	-10.00 [-20.26 , 0.26]
Jain 2019	39	11	30	50	14	30	6.0%	-11.00 [-17.37 , -4.63]
Javaherforooshzadeh 2018	38	7.7	30	55	8.1	30	9.0%	-17.00 [-21.00 , -13.00]
Khare 2018	39	15.3	30	47.3	8.2	30	6.2%	-8.30 [-14.51 , -2.09]
Khezri 2013	30	14.8	30	40	7.4	30	6.5%	-10.00 [-15.92 , -4.08]
Khezri 2013b	20	20	40	30	15	40	4.7%	-10.00 [-17.75 , -2.25]
Mowafi 2008	40	7.4	20	50	18.5	20	4.0%	-10.00 [-18.73 , -1.27]
Naguib 2006	10	5.3	100	27	10.8	100	11.4%	-17.00 [-19.36 , -14.64]
Norouzi 2019	52.9	17.5	44	66.5	3.7	44	7.2%	-13.60 [-18.89 , -8.31]
Patel 2015	33	13	36	42	13	36	6.4%	-9.00 [-15.01 , -2.99]
Seet 2015	22.3	22.7	36	22.7	23.8	37	3.0%	-0.40 [-11.07 , 10.27]
Turkistani 2007	45	17.5	30	60	10	15	4.5%	-15.00 [-23.05 , -6.95]
Subtotal (95% CI)			**538**			**528**	**81.8%**	**-11.58 [-14.08 , -9.08]**
Heterogeneity: Tau² = 11.38; Chi² = 30.72, df = 13 (P = 0.004); I² = 58%								
Test for overall effect: Z = 9.07 (P < 0.00001)								
1.1.2 Change VAS scores								
Naguib 1999	-9	2.9	25	4	11.2	25	8.2%	-13.00 [-17.54 , -8.46]
Naguib 2000	-7.7	11.3	36	3	11.3	12	5.0%	-10.70 [-18.08 , -3.32]
Pokharel 2014	-17	22.3	20	-14	22.2	20	2.0%	-3.00 [-16.79 , 10.79]
Torun 2019	-36.3	22	30	-22	20.7	30	3.0%	-14.30 [-25.11 , -3.49]
Subtotal (95% CI)			**111**			**87**	**18.2%**	**-11.96 [-15.48 , -8.45]**
Heterogeneity: Tau² = 0.00; Chi² = 2.12, df = 3 (P = 0.55); I² = 0%								
Test for overall effect: Z = 6.67 (P < 0.00001)								
Total (95% CI)			**649**			**615**	**100.0%**	**-11.69 [-13.80 , -9.59]**
Heterogeneity: Tau² = 8.74; Chi² = 33.57, df = 17 (P = 0.010); I² = 49%								
Test for overall effect: Z = 10.87 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.86), I² = 0%								



Based on individual primary study results (Table 3), 17 studies (Abbasivash 2019; Acil 2004; Ismail 2009; Jain 2019; Javaherforooshzadeh 2018; Khare 2018; Khezri 2013; Khezri 2013b; Khezri 2016; Mowafi 2008; Naguib 1999; Naguib 2000; Naguib 2006; Norouzi 2019; Patel 2015; Torun 2019; Turkistani 2007) reported a reduction in preoperative anxiety measured by VAS when comparing melatonin with placebo. When results (median (IQR) to mean (SD)) from one of these studies were extracted and converted (Ismail 2009), the effect of this study was lost because the 95% CI included the value of zero. Capuzzo 2006 showed no difference between melatonin and placebo in preoperative anxiety measured by a numerical rating scale (NRS). Two studies had wide 95% CIs and included the value of zero; hence these authors reported no difference between melatonin and placebo in preoperative anxiety measured by VAS (Pokharel 2014; Seet 2015). Two studies not included in the meta-analysis showed no difference between melatonin and placebo in preoperative anxiety measured by a modified six-item STAI (STAI-S) or a standard STAI, respectively (Hoseini 2015; Ionescu 2008).

We prepared a funnel plot for our primary meta-analysis (Figure 5; Analysis 1.1), which appeared symmetrical, indicating that publication bias was unlikely.

Figure 5. Funnel plot of comparison: 1 Melatonin versus placebo, outcome: 1.1 Preoperative anxiety (VAS) [mm].



We performed a separate sensitivity analysis when we excluded all studies that were assessed as having an overall high risk of bias. We excluded from meta-analysis four studies with an overall high risk of bias (Javaherforooshzadeh 2018; Khezri 2013; Norouzi 2019; Pokharel 2014). We found that melatonin reduced preoperative anxiety compared to placebo (MD -10.20, 95% CI -13.87 to -8.53; P < 0.00001, I^2 = 54%; 13 studies, 936 participants; Table 2).

To explore heterogeneity, we performed subgroup analysis based on anaesthetic modality, participants' age, and the dose of melatonin administered. It is not recommended to perform subgroup analysis if fewer than 10 studies are identified (Higgins 2019); hence, we performed subgroup analysis only on our primary outcome: preoperative anxiety melatonin versus placebo.

Anaesthetic modality

Eleven studies used general anaesthesia and showed a reduction in preoperative anxiety (MD -12.25, 95% CI -14.85 to -9.64; P < 0.00001, I^2 = 51%; 11 studies, 796 participants; Table 5). Six studies used topical, regional, or spinal anaesthesia and showed a reduction in preoperative anxiety (MD -10.97, 95% CI -13.91 to -8.02; P < 0.00001,

I^2 = 0%; 6 studies, 340 participants; Table 5). Capuzzo 2006 used general and spinal anaesthesia but did not provide information regarding anxiety measurements for each group; hence, this study was not included in the analysis. The test for subgroup differences indicated no statistically significant subgroup effect (P = 0.52; Table 5). It does not appear that anaesthetic modality alters effects of an intervention; however, fewer trials and participants contributed data to one subgroup (topical, regional, or spinal anaesthesia), meaning that the analysis might not be able to detect subgroup differences.

Age of participants (≤ 60 or > 60 years)

Three studies included only participants older than 60 years and showed a reduction in preoperative anxiety (MD -8.04, 95% CI -13.58 to -2.50; P = 0.004, I^2 = 0%; 3 studies, 258 participants; Table 5). Ismail 2009 included only patients over the age of 60, and Capuzzo 2006 included only patients over the age of 65. The remaining study included patients between 35 and 85 years of age (Khezri 2013b), but mean age was above 70 years, which is why this study was included in the > 60 years of age group. Khezri 2013 included patients 25 to 80 years of age. Mean age in the melatonin group was 63.50 ± 15.28; we decided to not include this study in subgroup analysis because it did not fit into either group (≤ 60 or > 60 years of age). Two studies also included patients over 60 years of age (Pokharel 2014; Seet 2015), but the mean age was way below 60 years, which is why these studies were included in the ≤ 60 years group.

Fourteen studies included patients younger than 60 years and also showed a reduction in preoperative anxiety when comparing melatonin to placebo (MD -12.36, 95% CI -14.62 to -10.09; P < 0.02, I^2 = 50%; 14 studies, 946 participants; Table 5). The test for subgroup differences did not reach statistical significance (P = 0.16; Table 5).

Dose of melatonin (< 6 mg or ≥ 6 mg)

We decided to divide studies into two groups depending on the dose of melatonin administered (< 6 mg or ≥ 6 mg).

Ten studies administered melatonin doses ≥ 6 mg and showed a reduction in preoperative anxiety compared to placebo (MD -12.28, 95% CI -15.21 to -9.35; P < 0.00001, I^2 = 57%; 10 studies, 735 participants; Table 5). Naguib 2006 administered 0.2 mg/kg melatonin, and Patel 2015 administered 0.4 mg/kg melatonin, but when the dose of melatonin was calculated based on mean weight in the melatonin groups, doses were above 6 mg of melatonin, which is why these studies where included in the ≥ 6 mg group. Torun 2019 administered melatonin at a dose of 0.4 mg/kg; however, this study provided no information regarding the mean weight of participants. We assumed that doses given were above 6 mg if participants weighed between 40 and 80 kg, which is why the study was included in the ≥ 6 mg group. Naguib 2000 administered different doses of melatonin (0.05, 0.1, 0.2 mg/kg); however, this study reported outcomes graphically, and it is not possible to distinguish the groups from one another, which is why this study was not included in subgroup analysis.

Seven studies administered < 6 mg of melatonin and showed a reduction in anxiety compared with placebo (MD -10.98, 95% CI -13.88 to -8.09; P < 0.00001, I^2 = 22%; 7 studies, 481 participants; Table 5).

The test for subgroup differences did not reach statistical significance (P = 0.16; Table 5).

Postoperative anxiety

Immediate postoperative anxiety (recovery room discharge to 90 minutes postoperatively)

The meta-analysis showed a difference in postoperative anxiety between the two groups (MD -5.04, 95% CI -9.52 to -0.55; P = 0.03, I^2 = 89; 7 studies, 524 participants; low-certainty evidence; Analysis 1.2); however, the 95% confidence interval was wide, which limited the certainty of evidence. When a sensitivity analysis was performed while excluding studies that did not report an SD or reported an SD value of 0, there was still a difference; however, the 95% confidence interval was wide (MD -4.31, 95% CI -7.18 to -1.44; P = 0.003, I^2 = 39; 4 studies, 246 participants; Table 4).

We performed an additional sensitivity analysis from which we excluded studies with an overall high risk of bias (Javaherforooshzadeh 2018; Khezri 2013; Khezri 2013b; Norouzi 2019; Pokharel 2014), and we found no difference in postoperative anxiety (MD -0.79, 95% CI -3.67 to 2.09; P = 0.70, I^2 = 0; 3 studies, 236 participants; Table 2).

Delayed postoperative anxiety (6 hours postoperatively)

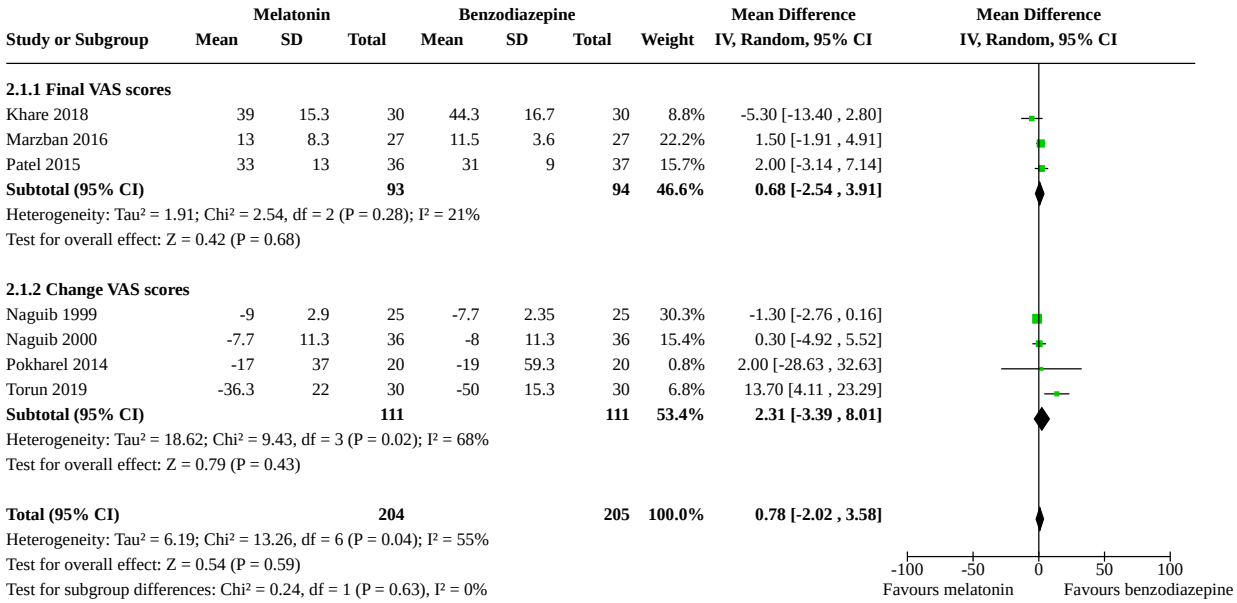
The meta-analysis (excluding two studies - Ionescu 2008 and Javaherforooshzadeh 2018) showed a reduction in postoperative anxiety (MD -5.31, 95% CI -8.78 to -1.84; P = 0.003, I^2 = 0; 2 studies, 73 participants; low-certainty evidence; Analysis 1.3). Ionescu 2008 also showed a reduction in postoperative anxiety measured six hours postoperatively in the melatonin group compared with the placebo group. Javaherforooshzadeh 2018 showed a reduction in postoperative anxiety measured six hours postoperatively.

Melatonin versus benzodiazepine

Preoperative anxiety

The meta-analysis showed no difference in preoperative anxiety between the two groups (MD 0.78, 95% CI -2.02 to 3.58; P = 0.59, I^2 = 55%; 7 studies, 409 participants; moderate-certainty evidence; Analysis 2.1; Figure 6). When performing sensitivity analysis excluding all studies reporting outcomes using IQR or range, while excluding one additional study because the study was not sufficiently blinded (Marzban 2016), we also found no difference in preoperative anxiety between the two groups (MD 0.91, 95% CI -3.02 to 4.83; P = 0.65, I^2 = 67%; 5 studies, 350 participants; Table 4).

Figure 6. Forest plot of comparison: 2 Melatonin versus benzodiazepine - preoperative anxiety, outcome: 2.1 Preoperative anxiety (VAS) [mm].



Based on individual primary study results (Table 3), none of the studies showed a difference between melatonin and benzodiazepine. Khare 2018 found that melatonin reduced anxiety more than alprazolam, but we could not reproduce this result from data extracted from the study. Marzban 2016 also stated that melatonin reduced anxiety more than midazolam; however, we could not reproduce this result. Khanna 2019 reported no difference in preoperative anxiety measured on the BAI when comparing melatonin with alprazolam.

We performed an additional sensitivity analysis from which we excluded all studies with an overall high risk of bias (Marzban 2016; Pokharel 2014). We found that melatonin did not decrease preoperative anxiety compared with benzodiazepines (MD 0.85, 95% CI -3.01 to 4.72; P = 0.67, I^2 = 66%; 5 studies, 315 participants; Table 2).

Postoperative anxiety

Immediate postoperative anxiety (recovery room discharge to 90 minutes postoperatively)

The meta-analysis showed no difference in postoperative anxiety between the two groups (MD -2.12, 95% CI -4.61 to 0.36; P = 0.09, I^2 = 0%; 3 studies, 176 participants; very low-certainty evidence; Analysis 2.2).

Ionescu 2008, using a modified version of STAI (the State scale - S-STAI) (which was not included in the meta-analysis because the scale used was not comparable to the VAS), reported a difference between melatonin and benzodiazepine one hour postoperatively. Khanna 2019 using the BAI showed no difference between alprazolam and melatonin one hour postoperatively.

Sensitivity analysis from which all studies with an overall high risk of bias were excluded - Marzban 2016 - showed no difference in postoperative anxiety (MD -2.02, 95% CI -5.82 to 1.78; P = 0.30, I^2 = 0%; 2 studies, 122 participants; Table 2).

Delayed postoperative anxiety (6 hours postoperatively)

Ionescu 2008 measured postoperative anxiety using a modified version of S-STAI six hours postoperatively and showed no difference between the two groups (Table 3). Dianatkhah 2015, using the Hamilton Anxiety Rating Scale (HAM-A) to measure anxiety after surgery, showed a difference between melatonin and oxazepam. Khanna 2019, using the BAI, showed no difference between alprazolam and melatonin six hours postoperatively.

DISCUSSION

Summary of main results

This systematic review identified 27 randomized controlled trials (RCTs) assessing melatonin for treating preoperative anxiety, postoperative anxiety, or both. Twenty-four of the 27 studies compared melatonin with placebo, and 11 studies compared melatonin with a benzodiazepine.

Melatonin versus placebo

We found moderate-certainty evidence, based on meta-analysis of 18 studies, to show that melatonin likely reduces preoperative anxiety compared to placebo. The previous version of this review found that melatonin decreased preoperative anxiety compared to placebo by 13 points on a visual analogue scale (VAS) (Hansen 2015). In this review update, we found a slightly smaller decrease of 12 points on a VAS.

Results of individual primary studies indicate that 16 of the 21 studies that assessed effects of melatonin on preoperative anxiety showed a reduction compared to placebo. Six studies did not show any differences between melatonin and placebo.

Fifteen studies assessed effects of melatonin on postoperative anxiety. Of these, 11 studies compared melatonin with placebo, and seven studies compared melatonin with a benzodiazepine.

We found low-certainty evidence, based on meta-analysis of seven studies, suggesting that melatonin may reduce immediate postoperative anxiety compared to placebo. However, the result was below our minimum clinically important difference. Low-certainty evidence, based on meta-analysis of two studies, suggests that melatonin may reduce delayed postoperative anxiety compared to placebo.

The previous review found no evidence of a decrease in postoperative anxiety when melatonin was compared to placebo (Hansen 2015). In contrast, in this review update, we found a decrease in immediate and delayed postoperative anxiety of 5 points on a VAS, but evidence was uncertain in the analysis, and the result was below our estimated minimum clinically important difference.

Melatonin versus benzodiazepine

We found moderate-certainty evidence, based on meta-analysis of seven studies, to show that melatonin may result in no difference in preoperative anxiety compared to benzodiazepines. None of the 11 studies that assessed effects of melatonin compared with a benzodiazepine on preoperative anxiety showed a difference.

Evidence on the effect of melatonin on immediate postoperative anxiety compared to benzodiazepines was very uncertain. No difference was seen in the meta-analysis of three studies.

Overall completeness and applicability of evidence

A minimum difference in preoperative and postoperative anxiety VAS score has not been fully established. However, with regard to acute pain VAS scores, it has been estimated that 9 to 14 mm on a 0 to 100 mm VAS is the minimum clinically significant difference (Kelly 1998; Kelly 2001). Thus, main results from the meta-analyses regarding preoperative anxiety when melatonin was compared with placebo (12 mm for primary meta-analysis and 12 mm for the sensitivity analysis) could be considered clinically relevant.

Whether the anxiolytic effect of melatonin can be applied to all surgical patients remains unclear, as many factors influence the risk of preoperative anxiety. Among these are age, sex, type of surgery, type of anaesthesia, and cultural and religious differences (Caumo 2001a; Domar 1989; Kindler 2000; Lovering 2006). Younger age and female sex have been shown to be independent risk factors for preoperative anxiety (Caumo 2001a; Domar 1989; Kindler 2000). This may influence the external validity of our results, as two of the studies in this review included only patients older than 60 years (Capuzzo 2006; Ismail 2009), and five of the studies in this review included only women (Caumo 2007; Caumo 2009; Khezri 2013; Naguib 1999; Naguib 2000).

Conflicting opinions can be found in the literature regarding preoperative anxiety and type of surgery. Caumo 2001a showed that medium or major surgery (classified according to blood loss, degree of pain, invasiveness, degree of monitoring required, and length of stay in hospital due to the surgical procedure) leads to higher preoperative anxiety. In contrast, Domar 1989 showed no difference regarding type of surgery and preoperative anxiety. The type of anaesthesia used - regional versus general - can also influence anxiety levels in different directions (Haugen 2009; Mitchell 2008; Mitchell 2010; Mitchell 2012). As far as general anaesthesia is concerned, many patients fear waking up during surgery or not waking up after surgery (Mitchell 2010; Ramsay 1972).

Furthermore, for the most part, general anaesthesia is used for major surgery, which in itself may influence the risk of anxiety (Caumo 2001a). As far as regional anaesthesia is concerned, patients experience the anxiety of being awake during the procedure, involving all the noises, lights, and pain associated with this (Mitchell 2008). The studies included in this review vary from minor to major surgery, performed with general, regional, or topical anaesthesia. We conducted three subgroup analyses exploring effects of anaesthetic modality, age of participants, and dose of melatonin on heterogeneity for our primary analysis: preoperative anxiety melatonin versus placebo. When anaesthetic modality was assessed, statistical heterogeneity presented as an I^2 value was close to equal to our primary analysis in the general anaesthesia group (I^2 = 51% in subgroup and I^2 = 49% in primary analysis). The effect estimate was close to our primary analysis as well (-12.25 in subgroup analysis and -11.69 in primary analysis). In the other group (topical, local, or spinal anaesthesia), statistical heterogeneity totally disappeared (I^2 = 0%), but the effect estimate was close to our primary analysis (-10.97). Testing for subgroup differences indicated no statistically significant subgroup effect (P = 0.52). However, there were far more studies in one of the subgroups, which is why the analysis might not be able to detect subgroup differences. It appears that anaesthetic modality does not explain the heterogeneity in our primary analysis.

In our subgroup analysis exploring the effect of participant age, it appears that melatonin has a lesser effect in an older population (> 60 years). Statistical heterogeneity disappeared in the group > 60 years of age (I^2 = 0). However, this subgroup included only three studies, so this conclusion cannot be made with certainty. These subgroup differences did not reach statistical significance; however, because one subgroup contained only three studies, the analysis might not be able to detect subgroup differences.

When the effect of the dose of melatonin administered was explored, statistical heterogeneity was still present in both the ≥ 6 mg group and the < 6 mg group (I^2 = 57% and I^2 = 22%, respectively). Effect estimates in both subgroups were close to our primary analysis (-12.28 in ≥ 6 mg group and -10.98 in < 6 mg group). Testing of subgroup differences did not reach statistical significance. The dose of melatonin did not explain heterogeneity in our primary analysis.

Cultural and religious differences have been shown to influence the actual perception of anxiety (Lovering 2006). Sixteen of the 25 studies were carried out in Middle Eastern countries (Saudi Arabia, Turkey, and Iran), one in Italy, one in Romania, two in Brazil, four in India, one in Singapore, and one in Nepal. This could lead to an imbalance and could influence external validity as some cultures are over-represented and others are under-represented.

In 21 of the 27 included studies, the method used to measure preoperative anxiety was the VAS (in one study, a numerical rating scale (NRS) (Capuzzo 2006)), and only three studies used the State-Trait Anxiety Inventory (STAI). The VAS and the STAI as anxiety-measuring techniques were used to measure preoperative and postoperative anxiety and have been validated in a surgical population (Kindler 2000). To date, the gold standard for anxiety evaluation is the STAI, but its architecture of 20 to 40 multiple choice

questions for anxiety alone limits its use as a bedside instrument. In contrast, the VAS allows patients to easily indicate their degree of preoperative or postoperative anxiety by simply marking a point on a horizontal line. The simple VAS method is very easily applied for both doctor and patient and has proved a useful and valid measure of preoperative anxiety (Kindler 2000; Millar 1995).

Of the 27 studies in our review, nine studies administered melatonin sublingually, and 18 administered it orally as tablets. With sublingual administration (comparable to intravenous administration), first-pass metabolism is bypassed, and this leads to variation in bioavailability compared to oral administration (Brzezinski 1997). Due to heterogeneity of the method of administration used by included studies, additional studies are required to perform relevant subgroup analyses.

Of the 15 studies assessing postoperative anxiety, only five studies measured anxiety six hours postoperatively, whereas the remaining studies mainly assessed anxiety in the immediate postoperative period. Hence, more studies are warranted to clearly determine effects of melatonin on postoperative anxiety in the postoperative period.

The half-life of melatonin was examined in a systematic review (Harpsoe 2015). This review included 22 studies that explored the pharmacokinetics of melatonin and concluded that the half-life of melatonin was approximately 45 minutes when melatonin was administered orally or intravenously. Heizmann 1983 examined the pharmacokinetics of midazolam in six healthy males. These investigators found that the half-life was 2.3 hours when given intravenously and was almost the same when given orally. This might have an effect on postoperative anxiety in that melatonin, benzodiazepines, and placebo were administered preoperatively. We found no difference in postoperative anxiety when melatonin was compared with benzodiazepines, whereas we found a small difference when melatonin was compared with placebo; however, this difference might not be clinically relevant. In future studies, melatonin could be administered in the immediate postoperative period to better determine the effect of melatonin on postoperative anxiety.

Quality of the evidence

Almost half of the included studies had low risk of selection bias, and at least 70% had low risk of attrition, performance, and detection bias. Most of the included studies had unclear risk of reporting bias; however, some had high risk because the protocol and the manuscript were not identical.

We performed sensitivity analyses for all primary and secondary outcomes when we excluded studies with overall high risk of bias to test the robustness of the estimated effect. We did not find that inclusion of studies with high risk of bias altered our conclusions, except for postoperative anxiety, when melatonin was compared with placebo. When studies with overall high risk of bias were excluded from this analysis, the effect was lost.

The estimate of effect for the primary outcome (preoperative anxiety) was judged as having evidence of moderate certainty, based on GRADE assessment, for the comparison of melatonin versus placebo and melatonin versus benzodiazepines. Evidence was downgraded by one level for our primary outcome preoperative anxiety for the comparison of melatonin versus placebo due to substantial heterogeneity and overall high risk of bias. However, sensitivity analysis from which all studies with overall high risk of bias were excluded showed a similar result as our main meta-analysis. Therefore, we chose to downgrade the certainty of evidence by only one level, because we concluded that inclusion of studies with high risk of bias did not alter conclusions. Evidence was downgraded by one level for the comparison of melatonin versus benzodiazepines for preoperative anxiety due to substantial heterogeneity and overall high risk of bias. The sensitivity analysis exploring whether studies with high risk of bias would alter the conclusions showed a similar result as the main analysis for this comparison. For this reason, we decided to downgrade by only one level. The estimate of effect for the secondary outcome (postoperative anxiety) was judged as having evidence of low certainty for melatonin versus placebo and for melatonin versus midazolam. This was due to large heterogeneity, small numbers of participants, and overall high risk of bias.

When exploring heterogeneity in our review, we found I^2 of 49% for our main analysis (Figure 4). We considered this to be moderate and not a substantial issue; hence, we performed only random-effects model meta-analyses. In the process of analysing the data, we also performed a sensitivity analysis (Table 4) by excluding studies that reported only median (interquartile range (IQR) or range) for VAS data on preoperative anxiety. The I^2 value for this sensitivity analysis was 34%. The statistical heterogeneity seen in our primary analysis is suspected to be due to clinical diversity. Studies varied in study design, population, anaesthesia, and type of surgery. We performed subgroup analysis by which we examined the effects of anaesthetic modality, dose of melatonin, and age of participants (Table 5); however, none of the subgroup analyses reached statistical significance upon testing for subgroup differences. When the different subgroups are examined, it appears that age of participants might explain some of the statistical heterogeneity found in our primary analysis. It appears that older age is an effect modifier; however, some unexplained heterogeneity is still present in our primary analysis, which we have not been able to explain through subgroup analysis.

Potential biases in the review process

To obtain additional information, we contacted the authors of 20 of the included studies. Four authors answered sufficiently (Capuzzo 2006; Dianatkhah 2015; Jain 2019; Marzban 2016), one author answered insufficiently (Ionescu 2008), and information regarding the remaining 15 studies was not obtained as study authors did not reply, despite repeated attempts. Khanna 2019 did not provide any contact information; hence, we were unable to contact study authors. This might have introduced a potential source of bias, in that some of these studies were excluded from meta-analysis or sensitivity analysis and therefore if included, could have altered the results.

Marzban 2016 was only single-blinded, which creates possible bias, but the remaining studies were double-blinded.

A single review author (BKM) performed data extraction in duplicate. Even though data extraction was done in duplicate, this could present a potential source of bias due to the possibility of duplicating the single review author's biases.

Ionescu 2008 used a short version of the STAI. The six-item STAI has been validated previously (Marteau 1992); however, we were

unable to retrieve a conversion key for this questionnaire and therefore decided not to include this study in the meta-analysis because we were unable to pool results across the two scales (STAI and six-item STAI).

Several studies did not report on adverse events; therefore it is not possible to conclude with certainty, from the data on adverse effects collected in this review, that melatonin is better tolerated than benzodiazepines. However, several studies reported that benzodiazepines caused impairment of psychomotor and cognitive functions, whereas melatonin, for the most part, did not, or did so to a lesser extent than benzodiazepines. So, it appears that melatonin is tolerated better than benzodiazepines.

When studies presented data only as graphs or figures, we read values directly from the graphs. This could have introduced minor errors because it is not particularly precise compared to other software methods. This could have introduced uncertainty to the exact results.

Agreements and disagreements with other studies or reviews

Two other systematic reviews have investigated the effect of melatonin as an anxiolytic in the perioperative period (Andersen 2014a; Yousaf 2010). Yousaf 2010 identified 10 studies investigating perioperative anxiety. These studies are also included in our review, together with 17 others (Abbasivash 2019; Dianatkhah 2015; Hoseini 2015; Jain 2019; Javaherforooshzadeh 2018; Khanna 2019; Khare 2018; Khezri 2013; Khezri 2013b; Khezri 2016; Marzban 2016; Norouzi 2019; Patel 2015; Pokharel 2014; Seet 2015; Torun 2019; Turkistani 2007). The study by Turkistani et al. was not included due to lack of a pre-intervention anxiety score (exclusion criterion). The rest of the studies were not included because they were published after the search date. We chose not to believe that lack of this specific assessment (pre-intervention anxiety score) should be considered a potential confounder due to the randomized design of all included studies; hence, this was not an exclusion criterion in our review. Andersen 2014a identified 14 studies investigating perioperative anxiety. Twelve of the studies included in that review are also included in our review (Acil 2004; Capuzzo 2006; Caumo 2007; Caumo 2009; Ionescu 2008; Ismail 2009; Khezri 2013; Mowafi 2008; Naguib 1999; Naguib 2000; Naguib 2006; Turkistani 2007); two studies examined anxiety in children and are not included in our review.

The findings of the reviews mentioned above - Yousaf 2010 and Andersen 2014a - and the findings of ours agree that melatonin premedication is effective in ameliorating perioperative anxiety. However, in Yousaf 2010, no quantitative analyses were undertaken. This was mainly explained by the fact that retrieved data were presented in a graphical fashion or as median and range. Furthermore, the review authors found the heterogeneity of the studies too extensive to synthesize the data quantitatively (Yousaf 2010). Andersen 2014a performed meta-analysis but explained that the analysis was very heterogeneous, which was partially resolved by the exclusion of studies in which median (IQR or range) was converted to mean (SD). Andersen 2014a included Acil 2004 in their meta-analysis; we chose not to include this one because the study did not report an SD.

Due to the review authors' assessment of heterogeneity (Yousaf 2010), they concluded that future studies should focus on investigating effects on more varied surgical populations and the optimal dosing regimen.

AUTHORS' CONCLUSIONS

Implications for practice

When compared with placebo, melatonin given as premedication (tablets or sublingually) likely reduces preoperative anxiety in adults (measured 50 to 120 minutes after administration). The almost 12-point reduction in anxiety observed could be considered clinically relevant and seems comparable to the reduction seen with benzodiazepines. Melatonin may be as effective as standard treatment with benzodiazepines in reducing preoperative anxiety in adults (measured 50 to 120 minutes after administration). Melatonin probably slightly reduces postoperative anxiety compared to placebo in adults, but the clinical relevance of this result is uncertain.

Implications for research

Future studies should include larger populations and should explore potential differences in effect based on age groups and biological sex. It appears that melatonin has lesser effect in an older population, which is why more studies including an older population are needed. Studies should be conducted in more countries, especially in Europe and North America, as these regions are under-represented in current evidence. More studies investigating specific types of anaesthesia and types of surgery are needed to clarify effects in different surgical populations. Even though we observed in this review that melatonin reduced anxiety compared to placebo, future studies could include larger doses of melatonin to explore their effects. To explore the prophylactic effects of melatonin on perioperative anxiety, future studies could also investigate the impact of providing daily treatment from approximately one week preoperatively until one week postoperatively. Few of the included studies provided information regarding postoperative anxiety, which is why future studies exploring effects of melatonin on postoperative anxiety are needed. When future studies are conducted, the adverse effect profile of melatonin should be investigated systematically and consistently, because several of the included studies failed to report adverse effects. In future studies, the effects of melatonin on cognitive and psychomotor functions could be investigated more consistently.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Abbasivash 2019

Study characteristics	
Methods	Randomized, double-blind, placebo-controlled study Location: Iran Study design: parallel, 2-armed (melatonin, placebo)
Participants	Total of 50 patients; 25 patients in each arm Age: melatonin 34.23 ± 9.05, placebo 31.68 ± 8.80 Sex: (M/F) in %: melatonin (48/52), placebo (44/56) ASA class: I to II Type of surgery: elective hand surgery such as carpal tunnel syndrome, trigger finger, release surgery, or tendon repair

Abbasivash 2019 *(Continued)*

	Type of anaesthesia: intravenous regional anaesthesia (IVRA) Baseline (anxiety, pain) described: no, no
Interventions	Melatonin: 6 mg Placebo Administration route: oral Time of administration: 90 minutes before surgery
Outcomes	• Tourniquet-induced pain measured by verbal pain score (VPS) (0 to 10) after the tourniquet is filled and at 10, 20, 30, 40, 50 minutes • Sensory block duration and motor block duration • Patient request for analgesia measured from the moment the tourniquet was emptied • Anxiety measured by a verbal anxiety score (VAS) (0 to 10) 90 minutes after premedication • Haemodynamics (MAP, HR, arterial oxygen saturation)
Notes	Sample size: described

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"To compensate shifting from normality in data distribution, 25 cases were used in each group, and using random allocation software, they were randomly divided into two groups of 25" (page 2) (Abbasivash 2019)
Allocation concealment (selection bias)	Unclear risk	"To compensate shifting from normality in data distribution, 25 cases were used in each group, and using random allocation software, they were randomly divided into two groups of 25" (page 2) No information regarding appearance of study drugs, or who performed allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No reported dropouts or missing data (Figure 1)
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"The drug[s] were placed in similar boxes with A and B labels, and the researcher was unaware of the group of each patient and became aware at the end of the study after collecting the data; also, the patients were not aware about the assigned groups" (page 2) No information regarding appearance of study drugs
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The drug[s] were placed in similar boxes with A and B labels, and the researcher was unaware of the group of each patient, and became aware at the end of the study after collecting the data" (page 2)
Other bias	Low risk	No other potential sources of bias encountered

Acil 2004

Study characteristics	
Methods	Randomized, double-blind, placebo-controlled study Location: Turkey Study design: parallel, 3-armed (melatonin, midazolam, placebo)
Participants	Total of 66 patients; 22 patients in each arm Age: melatonin 39.9 ± 7.5, midazolam 37.3 ± 7.8, placebo 39.2 ± 6.8 Sex: not described ASA class: I to II Type of surgery: elective laparoscopic cholecystectomy Type of anaesthesia: general Baseline (anxiety, pain) described: yes, no
Interventions	Melatonin: 5 mg Midazolam: 15 mg Placebo Administration route: sublingual Time of administration: 90 minutes before induction of general anaesthesia
Outcomes	• Anxiety measured by visual analogue scale (preoperative and postoperative) • Sedation score 1 to 4 • Orientation score 0 to 2 • Psychomotor performance measured with Trail Making A and B tests and the Word Fluency test ○ All outcomes were evaluated before (baseline) and 10, 30, 60, and 90 minutes after premedication had been given, and after the operation at 15, 30, 60, and 90 minutes in the recovery room • Pain measured by visual analogue scale • Satisfaction score (yes or no)
Notes	Sample size calculation: not described Study author (Karagöz) contacted by e-mail on 1 October 2019 to clarify unspecified issues: no reply

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information provided; described as randomized
Allocation concealment (selection bias)	Unclear risk	No information provided

Acil 2004 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	No reported dropouts or missing data
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information on taste of study drug not provided
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "a doctor blinded to the group assignment performed all tests" (page 554) (Acil 2004)
Other bias	Unclear risk	Quote: "in all groups, the patients were comparable in terms of age, weight, duration of surgery and anaesthesia" (page 554) No information regarding distribution of males and females

Capuzzo 2006

Study characteristics	
Methods	Randomized, double-blind, placebo-controlled study Location: Italy Study design: parallel, 2-armed
Participants	Total of 150 patients randomized; 12 did not complete 138 patients completed: 67 in melatonin group and 71 in placebo group Age: melatonin 73.2 ± 5.9, placebo 72.1 ± 5.4 Sex (M/F) in %: melatonin (48/52), placebo (52/48) ASA class: I to III Type of surgery: elective surgery Type of anaesthesia: general or spinal Baseline (anxiety, pain) described: yes, yes
Interventions	Melatonin: 10 mg Placebo Administration route: oral Time of administration: 90 minutes preoperatively
Outcomes	• Anxiety measured by numerical rating scale (0 to 10) (preoperative and postoperative) • Depression measured by numerical rating scale (0 to 10) • Pain measured by numerical rating scale (0 to 10)

Capuzzo 2006 *(Continued)*

	• Satisfaction with anaesthesia (0 to 100) • Cognitive function (Frontal Assessment Battery and Babcock Story Recall Test)
Notes	Sample size calculation: described Study author (M. Capuzzo) contacted by email in previous review (4 July 2013): investigators and assessors blinded. Mistake in dropout numbers in the 2 groups; should be 4 in the placebo group and 8 in the melatonin group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "the pharmacist prepared, by computer-generated randomization, 150 sealed envelopes, each reporting a code number and containing 2 capsules. Each indistinguishable capsule contained either 5 mg melatonin or placebo" (page 121) (Capuzzo 2006)
Allocation concealment (selection bias)	Low risk	Quote: "the pharmacist prepared, by computer-generated randomization, 150 sealed envelopes, each reporting a code number and containing 2 capsules. Each indistinguishable capsule contained either 5 mg melatonin or placebo" (page 121)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Patients not completing the study were almost balanced in numbers across intervention groups and had similar reasons for lack of completion
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patients and personnel blinded Quote: "indistinguishable capsules" (page 121)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors and investigator blinded (confirmed by email contact with study author)
Other bias	Low risk	No other sources of bias encountered

Caumo 2007

Study characteristics

Methods	Randomized, double-blind, placebo-controlled study Location: Brazil Study design: parallel, 2-armed
Participants	Total of 35 patients randomized; 2 did not complete 33 patients completed: 17 in melatonin group, 16 in placebo group Age: melatonin 44.82 ± 4.58, placebo 43.88 ± 4.09

Caumo 2007 *(Continued)*

	Sex (M/F) in %: melatonin (0/100), placebo (0/100) ASA class: I to III Type of surgery: abdominal hysterectomy Type af anaesthesia: general and epidural Baseline (anxiety, pain) described: yes, yes
Interventions	Melatonin: 5 mg Placebo Administration route: oral Time of administration: 10:00 PM the night before surgery and 1 hour preoperatively
Outcomes	• Postoperative pain assessed by pain scores (100-mm visual analogue scale) • Postoperative pain assessed by analgesic consumption (morphine in patient-controlled analgesia) • Rest-activity cycles measured by actigraphy • Anxiety assessed by State-Trait Anxiety Inventory (postoperative)
Notes	Sample size calculation: described Study author contacted by email on 15 July 2019 to clarify unspecified issues: no answer

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "... using a random number table..." (page 1264) (Caumo 2007)
Allocation concealment (selection bias)	Low risk	Quote: "blinding and randomization were performed by two investigators not involved in the patient evaluations" (page 1264)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "two patients, however, were excluded for major protocol violations" (page 1266)
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Adequately described in the article
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Adequately described in the article
Other bias	Low risk	No other sources of bias encountered

Caumo 2009

Study characteristics	
Methods	Randomized, double-blind, placebo-controlled study Location: Brazil Study design: parallel, 3-armed
Participants	Total of 63 patients randomized; 4 did not complete 59 patients completed: 20 in melatonin group, 19 in clonidine group, 20 in placebo group Age: melatonin 43.40 ± 5.48, clonidine 45.26 ± 3.40, placebo 45.35 ± 5.67 Sex (M/F) in %: melatonin: (0/100), clonidine (0/100), placebo (0/100) ASA class: I to III Type of surgery: abdominal hysterectomy Type af anaesthesia: general and epidural
Interventions	Melatonin: 5 mg Clonidine: 100 µg Placebo Administration route: oral Time of administration: 10:00 PM the night before surgery and 1 hour preoperatively for melatonin and placebo. For clonidine, an extra dose was given 36 hours postoperatively and both melatonin and placebo groups received placebo at this time
Outcomes	• Postoperative pain assessed by pain scores (100-mm visual analogue scale) • Postoperative pain assessed by analgesic consumption (morphine in patient-controlled analgesia) • Anxiety assessed by State-Trait Anxiety Inventory (postoperative)
Notes	Sample size calculation: described Study author contacted by email on 15 July 2019 to clarify unspecified issues: no answer

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Adequately described in the article
Allocation concealment (selection bias)	Low risk	Quote: "during the entire protocol timeline, blinding and randomization were undertaken by 2 investigators who were not involved in the patient's evaluation" (page 101) (Caumo 2009)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Flow diagram (Figure 1) shows the 4 patients who did not complete and reasons Quote: "...were excluded from analysis..." (page 103)

Caumo 2009 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "during the entire protocol timeline, blinding and randomization were undertaken by 2 investigators who were not involved in the patient's evaluation. Other individuals involved in the patient's care were unaware of the treatment group to which the patient belonged" (page 101)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "to ensure blinding, postoperative assessment was performed by a different physician from the one who carried out the preoperative evaluation" (page 101)
Other bias	Low risk	Quote: "demographic and morphometric characteristics were similar in patients assigned to receive melatonin, clonidine and placebo" (page 103) No other potential sources of bias encountered

Dianatkhah 2015

Study characteristics	
Methods	Randomized, double-blind study Location: Iran Study design: parallel, 2-armed
Participants	Total of 145 patients randomized 137 patients completed: 66 in melatonin group, 71 in oxazepam group Age: melatonin 60.03 ± 10.21, oxazepam 61.70 ± 9.86 Sex (M/F): melatonin 53/13, oxazepam 52/19 ASA class: not described Type of surgery: coronary artery bypass graft surgery (CABG) Type of anaesthesia: not described Baseline (anxiety, pain) described: no, no
Interventions	Melatonin: 3 mg Oxazepam: 10 mg Administration route: not described Time of administration: 1 hour before assigned sleep time, starting 3 days before surgery and until discharge
Outcomes	• Sleep quality evaluated using the Groningen Sleep Quality Score (GSQS) (15 questions regarding previous night's sleep quality) (preoperative and postoperative) • Anxiety assessed using the Hamilton Anxiety Rating Scale (HAM-A) - a 14-item questionnaire by which symptoms are graded on a scale of 0 to 4 • Delirium assessed by clinical observations from trained nurses

Dianatkhah 2015 *(Continued)*

Notes	Sample size calculation: described Study author contacted by email on 15 July 2019 to clarify unspecified issues: the correct protocol ID is IRCT 201303148698N11. Researcher, data collector, analyser, and patients were all blinded. Tablets were all the same in shape, size, and colour. A nurse was responsible for coding and distributing the tablets based on block number randomization

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "patients were allocated to each group using the permuted block randomization method…" (page 123) (Dianatkhah 2015)
Allocation concealment (selection bias)	Low risk	Study author was contacted by email and informed that both melatonin and oxazepam tablets were the same in shape, size, and colour. A nurse was responsible for coding oxazepam and melatonin and for giving them to patients based on block number randomization
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "…8 (5.5%) patients were excluded from the trial due to postoperative complications" (page 124) (Dianatkhah 2015)
Selective reporting (reporting bias)	High risk	Protocol is provided; however it is not found in the IRCT database. Study author was contacted by email and provided the correct protocol ID. Several other outcomes are listed in the article than in the protocol
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No information provided in the article. Study author was contacted by email and informed that both patients and personnel were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No information provided in the article. Study author was contacted by email and informed that both patients and personnel were blinded
Other bias	Unclear risk	Overweight of males in the study; however similar distribution of sex in melatonin and oxazepam groups

Hoseini 2015

Study characteristics

Methods	Randomized, double-blind, placebo-controlled study Location: Iran Study design: parallel, 4-armed
Participants	Total of 88 patients randomized 88 patients completed: 22 in melatonin group, 22 in clonidine group, 22 in gabapentin group, 22 in placebo group Age: melatonin 39.45 ± 11.40, clonidine 44.14 ± 8.41, gabapentin 40.50 ± 8.38, placebo 38.14 ± 10.80 Sex (M/F) in %: not adequately described

Hoseini 2015 *(Continued)*

	ASA class: I to II Type of surgery: laparoscopic cholecystectomy Type of anaesthesia: general Baseline (anxiety, pain) described: no, no
Interventions	Melatonin: 6 mg Clonidine: 0.2 mg Gabapentin: 600 mg Placebo Administration route: oral Time of administration: 120 minutes before surgery
Outcomes	• Postoperative pain assessed using a visual analogue scale (VAS) at 1, 2, 6, 12, and 24 hours postoperatively • Preoperative anxiety using State-Trait Anxiety Inventory (STAI) measured just before entry into operating room • Haemodynamics (heart rate; systolic, diastolic, and mean arterial blood pressure) • Time of receiving first dose of morphine and total amount of morphine administered during first 24 hours • Frequency of vomiting and intensity of postoperative nausea and vomiting (PONV) during first 24 hours
Notes	Sample size calculation: described

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "the allocation of treatment was done according to table of random numbers numbers with random block sampling…" (page 121) (Hoseini 2015)
Allocation concealment (selection bias)	Low risk	Quote: "the investigational drugs or placebo related to each patient had been prepared by pharmacy according to random allocation table in shape of uniform capsules…" (page 121)
Incomplete outcome data (attrition bias) All outcomes	Low risk	No reported dropouts or missing data
Selective reporting (reporting bias)	High risk	Protocol available. No secondary outcomes are mentioned in the protocol; however in the study, researchers analyse narcotic use during surgery, frequency of vomiting, severity of nausea, need for morphine, and haemodynamics
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "…both researchers and patients were blinded to the pre-treatment" (page 121)

Hoseini 2015 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "…both researchers and patients were blinded to the pre-treatment" (page 121)
Other bias	Low risk	Quote: "the study did not show significant differences between intervention groups in terms of age and sex and BMI" (page 122) No other potential sources of bias encountered

Ionescu 2008

Study characteristics	
Methods	Randomized, double-blind, placebo-controlled study Location: Romania Study design: parallel, 3-armed
Participants	Total of 53 patients randomized 53 patients completed: 18 in melatonin group, 17 in midazolam group, 18 in placebo group Age: melatonin 43.05 ± 11.40, midazolam 48.76 ± 12.61, placebo 48.38 ± 10.11 Sex (M/F) in %: not adequately described ASA class: I to II Type of surgery: laparoscopic cholecystectomy Type of anaesthesia: general Baseline (anxiety, pain) described: no, no
Interventions	Melatonin: 3 mg Midazolam: 3.75 mg Placebo Administration route: sublingual Time of administration: the night before surgery and 90 minutes preoperatively
Outcomes	• Sedation assessed by score 1 to 4 • Anxiety assessed by CD Spielberger's questionnaire, State-Trait Anxiety Inventory (STAI-S) (preoperative and postoperative) • Quality of postoperative sleep (good sleep, insomnia, nightmares) • Amnesia after recovery from anaesthesia (5 pictures) • Postoperative pain assessed by a visual analogue scale - verbal rating (1 to 5) • Intraoperative fentanyl requirements
Notes	Sample size calculation: described but not adequately

Ionescu 2008 *(Continued)*

	Study author contacted by email on 1 October 2019 to clarify unspecified issues: sample size was based on a small pilot study from which results were never published. Randomization was not performed using a random generator; other methods were not specified

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "...randomly allocated..." (page 9) (Ionescu 2008)
Allocation concealment (selection bias)	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	No reported dropouts or missing data
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "to maintain the double-blind nature of the study, the syringes were unmarked" (page 9)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "a registrar blinded to the group assignment performed all the tests" (page 9)
Other bias	Unclear risk	Quote: "there were no between-group differences with respect to age, weight, duration of surgery, and anaesthesia" (page 9) Distribution of sex not adequately described. Appears to be overweight among all groups of either males or females

Ismail 2009

Study characteristics	
Methods	Randomized, double-blind, placebo-controlled study Location: Saudi Arabia Study design: parallel, 2-armed
Participants	Total of 40 patients randomized 40 patients completed: 20 in melatonin group, 20 in placebo group Age: melatonin 72.8 ± 8.1, placebo 68.5 ± 7.9 Sex (M/F) in %: melatonin (55/45), placebo (50/50) ASA class: I to III Type of surgery: cataract surgery Type of anaesthesia: topical

Ismail 2009 *(Continued)*

	Baseline (anxiety, pain) described: yes, no
Interventions	Melatonin: 10 mg Placebo Administration route: oral Time of administration: 90 minutes preoperatively
Outcomes	• Anxiety assessed by verbal anxiety score (0 to 10) (preoperative) • Pain assessed by verbal pain score (0 to 10) • Analgesic consumption by fentanyl requirements • Intraocular pressure (IOP) measured by Shioetz tonometer • Haemodynamcis (heart rate and mean arterial pressure)
Notes	Sample size calculation: described Study author contacted by email 15 July 2019 to clarify unspecified issues: no reply

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomly allocated using an online research randomizer..." (page 1147) (Ismail 2009)
Allocation concealment (selection bias)	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	No reported dropouts or missing data
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "an ophthalmologist who was blinded..." and "...the operating surgeon, who was blinded to patient allocation..." and "the attending anaesthesiologist who was unaware of patient group assignment..." (page 1147)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "the attending anaesthesiologist who was unaware of patient group assignment managed the patients and recorded all data" (page 1147)
Other bias	Low risk	Quote: "there was no significant differences between the two groups with regard to age, weight, height, gender and duration of surgery (Table 1). There were also no significant differences in the baseline HR, MAP, IOP and anxiety scores" (page 1147) No additional sources of bias encountered

Jain 2019

Study characteristics	
Methods	Randomized, double-blind, placebo-controlled study Location: India Study design: parallel, 2-armed
Participants	Total of 60 patients randomized 60 patients completed: 30 in melatonin group, 30 in placebo group Age: melatonin 33.93 ± 8.97, placebo 38.07 ± 6.05 Sex (M/F): melatonin (15/15), placebo (13/17) ASA class: I to II Type of surgery: elective surgery longer than 30 minutes in duration Type of anaesthesia: general Baseline (anxiety, pain) described: yes, no
Interventions	Melatonin: 6 mg Placebo: vitamin D3 Administration route: oral Time of administration: 120 minutes before induction
Outcomes	• Requirement of propofol for induction of general anaesthesia • Anxiety assessed using a visual analogue scale (VAS) (0 = completely calm, 10 = the worst possible anxiety) preoperatively • Haemodynamics parameters during intubation and laryngoscopy
Notes	Sample size calculation: described Study author (Tanmay Tiwari) contacted 1 October to clarify unspecified issues: data were collected by a resident blinded to groups

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "the patients were divided…by using a computer-generated random number table" (page 17) (Jain 2019)
Allocation concealment (selection bias)	Unclear risk	Quote: "…the study medications were packaged in an identical manner and provided to the anesthesiologist in a thick opaque envelope" (page 17) No information regarding blinding of personnel enrolling patients
Incomplete outcome data (attrition bias) All outcomes	Low risk	No reported dropouts or missing data

Jain 2019 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No protocol available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "to ensure that the patients and anesthesiologist were blinded to the group assigned, the study medications were packaged in an identical manner and provided to the anesthesiologist in a thick opaque envelope" (page 17)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Informed by email correspondence with study author: data were collected by a resident blinded to groups
Other bias	Low risk	Quote: "demographic characteristics including age, gender, weight, ASA physical status, duration of surgery, and baseline BIS score were similar between the groups" (page 18) No additional sources of bias encountered

Javaherforooshzadeh 2018

Study characteristics	
Methods	Randomized, double-blind, placebo-controlled study Location: Iran Study design: parallel, 3-armed
Participants	Total of 90 patients randomized 90 patients completed: 30 in melatonin group, 30 in gabapentin group, 30 in placebo group Age: melatonin 49 ± 4.7, gabapentin 45 ± 6.1, placebo 48 ± 5.6 Sex (M/F): melatonin (13/17), gabapentin (14/16), placebo (15/15) ASA class: I to II Type of surgery: spinal surgery at 2 or 3 levels of laminectomy Type of anaesthesia: general Baseline (anxiety, pain) described: no, no
Interventions	Melatonin: 6 mg Gabapentin: 600 mg Placebo Administration route: oral Time of administration: 100 minutes before induction of anaesthesia
Outcomes	• Anxiety assessed using a verbal analogue scale (0 = completely calm, 10 = worst possible anxiety) (preoperative and postoperative) • Pain intensity assessed using a numerical visual analogue scale (0 to 10) (postoperative)

Javaherforooshzadeh 2018 *(Continued)*

	• First request for pain relief medication (minutes) and total amount of pethidine administered during first 24 hours • Patient satisfaction from analgesia qualitatively (excellent, good, moderate, and inappropriate equal to 4, 3, 2, and 1, separately)
Notes	Sample size calculation: described

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "participants were randomly allocated to three groups by using a computer-based randomization program…" (page 2) (Javaherforooshzadeh 2018)
Allocation concealment (selection bias)	Unclear risk	Quote: "…patients and outcome evaluators were blinded, however, not the investigators due to the nature of the interventions" (page 2) No information regarding personnel including patients in the study and if they were able to foresee allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Flow diagram (Figure 1) shows that no patients were lost to follow-up
Selective reporting (reporting bias)	High risk	Study protocol available Quote: "…has been registered at the Iranian Registry of Clinical Trials (IRCT ID: IRCT2017100436566N1)" (page 3) However, several more outcomes are listed in the manuscript than in the protocol (request for pain relief, patient satisfaction)
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "…patients and outcome evaluators were blinded, however, not the investigators due to the nature of the interventions" (page 2)
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "…patients and outcome evaluators were blinded, however, not the investigators due to the nature of the interventions" (page 2)
Other bias	Low risk	Quote: "no statistically significant differences between groups were found in patients' demographic and clinical characteristics and ASA class" (page 4) No additional sources of bias encountered

Khanna 2019

Study characteristics

Methods	Randomized controlled trial Location: India Study design: parallel, 3-armed
Participants	Total of 150 patients randomized

Khanna 2019 *(Continued)*

	50 patients in melatonin group, 50 patients in alprazolam group, 50 patients in pregabalin group Age: melatonin 33.5 ± 10.19, alprazolam 35.9 ± 8.71, pregabalin 34.7 ± 8.31 Gender (M/F): no information provided ASA class: I to II Type of surgery: laparoscopic surgery Type of anaesthesia: general Baseline (anxiety, pain) described: yes, no
Interventions	Melatonin: 3 mg Alprazolam: 0.5 mg Pregabalin: 75 mg Administration route: oral Time of administration: 1 hour before induction
Outcomes	• Preoperative and postoperative anxiety assessed using the Beck Anxiety Inventory score • Sedation assessed using Observer Assessment of Alertness/Sedation score (OAA/S) • Postoperative pain
Notes	Sample size: not described No contact information provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	No reported dropouts or missing data
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided.
Other bias	Unclear risk	No information regarding distribution of sex provided

Khare 2018

Study characteristics	
Methods	Randomized placebo-controlled study Location: India Study design: parallel, 3-armed
Participants	Total of 90 patients randomized 90 patients completed: 30 in melatonin group, 30 in alprazolam group, 30 in placebo group Age: melatonin 29.96 ± 10.152, alprazolam 28.53 ± 10.737, placebo 25.16 ± 2.01 Gender (M/F): melatonin (10/20), gabapentin (9/21), placebo (8/22) ASA class: I to II Type of surgery: various elective surgeries of > 1 hour duration Type of anaesthesia: general Baseline (anxiety, pain) described: yes, no
Interventions	Melatonin: 3 mg Alprazolam: 0.25 mg Placebo: low-dose multi-vitamin tablets Administration route: oral Time of administration: 120 minutes before induction of anaesthesia
Outcomes	• Anxiety assessed using a numerical VAS scale (0 = no anxiety, 10 = worst imaginable anxiety) (preoperative) • Sedation assessed using the Ramsey Sedation Score (RSS) (preoperative and postoperative) • Orientation assessed using a 3-point scale (0 to 2) (preoperative and postoperative) • Cognitive performance was assessed using the Digit Symbol Substitution Test (DSST) (preoperative and postoperative)
Notes	Sample size calculation: described Study author contacted by email 1 October 2019 to specify unspecified issues: no reply

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "the study participants were randomly allocated into three groups of 30 each using computer-generated table of random numbers" (page 658)
Allocation concealment (selection bias)	Unclear risk	Quote: "the study medication were given… in a closed, opaque identical-sealed envelope by the resident anesthesiologist" (page 659) No information provided regarding whether study personnel were able to foresee assignment

Khare 2018 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	No reported dropouts or missing data
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information on blinding of personnel provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information on blinding of personnel provided
Other bias	High risk	Overweight of females; however similar in all groups. Also placebo group younger than melatonin and alprazolam groups

Khezri 2013

Study characteristics	
Methods	Randomized, double-blind, placebo-controlled study Location: Iran Study design: parallel, 2-armed
Participants	Total of 60 patients randomized 60 patients completed: 30 in melatonin group, 30 in placebo group Age: melatonin 63.5 ± 15.28, placebo 70.38 ± 13.48 Gender (M/F) in %: melatonin (40/60), placebo (57/43) ASA class: I to III Type of surgery: cataract surgery Type of anaesthesia: topical Baseline (anxiety, pain) described: yes, yes
Interventions	Melatonin: 3 mg Placebo Administration route: sublingual Time of administration: 60 minutes preoperatively
Outcomes	• Anxiety assessed by verbal anxiety score (0 = completely calm to 10 = worst possible anxiety) (preoperative and postoperative) • Pain assessed by verbal pain score (0 to 10) • Intraoperative conditions assessed by scale

Khezri 2013 *(Continued)*

	• Intraocular pressure (IOP) measured by Shioetz tonometer • Haemodynamcis (heart rate, systolic blood pressure, diastolic blood pressure) • Analgesic consumption by fentanyl requirements
Notes	Sample size calculation: described Study author contacted by email on 15 July 2019 to clarify unspecified issues: no reply

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "using a computer-generated randomization schedule..." (page 320) (Khezri 2013)
Allocation concealment (selection bias)	Low risk	Quote: "patients were given the study drugs by a nurse who was unaware of the study" (page 320)
Incomplete outcome data (attrition bias) All outcomes	Low risk	No reported dropouts or missing data
Selective reporting (reporting bias)	High risk	Outcomes listed in the Iranian Registry of Clinical Trials (IRCT201102223051N3) are reported in the article. In addition, 2 other outcomes are reported in the article (analgesic consumption and intraoperative conditions). The trial registration number is not mentioned in the article
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "...a nurse who was unaware of the study" (page 320) "The ophthalmologist, who was blinded to the group..." (page 320) "...in which the patients, investigators, anaesthesiologist, and the surgeon were blinded to the given treatment..." (page 320)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "the ophthalmologist, who was blinded to the group..." (page 320) "...in which the patients, investigators, anaesthesiologist, and the surgeon were blinded to the given treatment..." (page 320)
Other bias	Unclear risk	Overweight men; however similar in both groups. Placebo group older than melatonin group No other sources of bias encountered

Khezri 2013b

Study characteristics

Methods	Randomized, double-blind, placebo-controlled study Location: Iran Study design: parallel, 3-armed
Participants	Total of 120 patients randomized 120 patients completed: 40 in melatonin group, 40 in gabapentin group, 40 in placebo group

Khezri 2013b *(Continued)*

	Age: melatonin 73.46 ± 11.30, gabapentin 75.6 ± 10.07, placebo 72.88 ± 10.76 Gender (M/F): melatonin (25/15), gabapentin (23/17), placebo (24/16) ASA class: I to III Type of surgery: cataract surgery Type of anaesthesia: topical Baseline (anxiety, pain) described: yes, yes
Interventions	Melatonin: 6 mg Gabapentin: 600 mg Placebo Administration route: oral Time of administration: 90 minutes before arrival in the operating room
Outcomes	• Pain assessed using a verbal pain scale (VPS) (0 = no pain, 10 = worst pain imaginable) (preoperative and postoperative) • Anxiety assessed using a verbal anxiety score (VAS) (0 = completely calm, 10 = worst possible anxiety) preoperative and postoperative) • Sedation level of patients during performance of retrobulbar block (4-point scale, 0 to 3) • Haemodynamics (MAP and HR) • Surgeon satisfaction after surgery (3-point scale: very bad, moderate, good)
Notes	Sample size calculation: described Study author contacted by email on 15 July 2019 to clarify unspecified issues: no answer

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomization was based on computer-generated codes" (page 582) (Khezri 2013b)
Allocation concealment (selection bias)	Low risk	Quote: "allocation was managed by a resident external to the project, and the study drugs were given by a nurse noninvolved in the study" (page 582)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Flow diagram (Figure 1) shows that no patients were lost to follow-up
Selective reporting (reporting bias)	High risk	Study protocol available (NCT01200641). In the protocol, researchers state that they will include 90 patients; however in the study they included 120 patients
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "the Anesthetist was blinded to the patient's group assignment, and the study data were recorded by a blinded observer. The study drugs were administered by a nurse who was noninvolved in this project" (page 582)

Khezri 2013b *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "...the study data were recorded by a blinded observer" (page 582)
Other bias	Unclear risk	Overweight of men; however, similar in all groups No other sources of bias encountered

Khezri 2016

Study characteristics	
Methods	Randomized, double-blind, placebo-controlled study Location: Iran Study design: parallel, 3-armed
Participants	Total of 120 patients randomized 120 patients completed: 40 in melatonin group (3 mg), 40 in melatonin group (6 mg), 40 in placebo group Age: melatonin (3 mg) 28.19 ± 6.21, melatonin (6 mg) 28.38 ± 5.67, placebo 28.63 ± 5.31 Gender (M/F): all female ASA class: I to II Type of surgery: cesarean section Type of anaesthesia: spinal Baseline (anxiety, pain) described: yes, no
Interventions	Melatonin: 3 mg Melatonin: 6 mg Placebo Administration route: sublingual Time of administration: 20 minutes before spinal anaesthesia
Outcomes	• Anxiety assessed using a verbal anxiety score (0 = completely calm, 10 = worst possible anxiety) (preoperatively and postoperatively) • Time to first requirement of analgesic supplement in first 24 postoperative hours • Total analgesic consumption in first 24 postoperative hours • Haemodynamics • Pain assessed using a numerical verbal pain scale (0 = no pain, 10 = maximum imaginable pain) (preoperatively)
Notes	Sample size calculation: described Study author contacted by email on 15 July 2019 to clarify unspecified issues: no reply

Khezri 2016 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomization was undertaken by means of computer generated random number…" (page 964) (Khezri 2016)
Allocation concealment (selection bias)	Low risk	Quote: "randomization was undertaken by means of computer generated random number in sealed opaque envelopes. Allocation was managed by a resident external to the project…" (page 964)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Flow diagram (Figure 1) shows that no patients were lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "… the study drugs given by a nurse non-involved in the study. The anesthetist was blinded to the patient's group assignment…" (page 964)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "…the study data were recorded by a blinded observer..." (page 964)
Other bias	Low risk	Quote: "no significant differences in age, stature, and weight among the three groups were found. The duration of surgery was also similar" (page 966) No other sources of bias encountered

Marzban 2016

Study characteristics	
Methods	Randomized, single-blind trial Location: Iran Study design: parallel, 3-armed
Participants	Total of 81 patients randomized 81 patients completed: 27 in melatonin group, 27 in gabapentin group, 27 in placebo/midazolam group Age: melatonin 58 ± 7, gabapentin 53 ± 6, placebo/midazolam 55 ± 8 Gender (M/F) in %: melatonin (37/63), gabapentin (44/56), placebo/midazolam (66.7/33.3) ASA class: I to III Type of surgery: cataract surgery Type of anaesthesia: topical Baseline (anxiety, pain) described: yes, yes

Marzban 2016 *(Continued)*

Interventions	Melatonin: 6-mg tablet (90 minutes before surgery) Gabapentin: 600-mg capsule (90 minutes before surgery) Placebo: placebo (90 minutes before surgery) and 1 mg midazolam (just before surgery) Administration route: oral route (melatonin, gabapentin, placebo), IV route midazolam Time of administration: 90 minutes before arrival to operation room (gabapentin, melatonin, placebo)
Outcomes	• Anxiety assessed using a verbal anxiety score (VAS) (0 to 10) preoperatively and postoperatively • Pain assessed using a verbal pain score (VPS) (0 to 10) preoperatively and postoperatively • Sedation • Haemodynamics: heart rate and mean arterial pressure
Notes	Sample size: described but inadequately Study author (S. Haddadi) contacted by email: patients, the evaluator, and the ophthalmologist were not aware of the type of medication prescribed Only the anaesthesiologist was aware in case of possible side effects, so he could cure them immediately. Patients were randomized by random allocation method divided into 3 groups

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Informed by email correspondence: Patients were randomized by random allocation method divided into 3 groups; other information not provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	No reported dropouts or missing data
Selective reporting (reporting bias)	Unclear risk	Study protocol available (IRCT2015031121436N1)
Blinding of participants and personnel (performance bias) All outcomes	High risk	Informed by email correspondence: patients, the evaluator, and the ophthalmologist were not aware of the type of medication prescribed Only the anaesthesiologist was aware in case of possible side effects, so he could cure them immediately
Blinding of outcome assessment (detection bias) All outcomes	High risk	Informed by email correspondence: patients, the evaluator, and the ophthalmologist were not aware of the type of medication prescribed Only the anaesthesiologist was aware in case of possible side effects, so he could cure them immediately
Other bias	High risk	Overweight of females in placebo and gabapentin groups, whereas overweight of males in placebo/midazolam group

Mowafi 2008

Study characteristics	
Methods	Randomized, double-blind, placebo-controlled study Location: Saudi Arabia Study design: parallel, 2-armed
Participants	Total of 40 patients randomized 40 patients completed: 20 in melatonin group, 20 in placebo group Age: melatonin 44.6 ± 11.4, placebo 42.8 ± 12.1 Gender (M/F) in %: melatonin (60/40), placebo (50/50) ASA class: I to II Type of surgery: hand surgery (i.e. carpal tunnel, trigger finger, tendon release, or cut tendon repair) Type of anaesthesia: regional Baseline (anxiety, pain) described: yes, yes
Interventions	Melatonin: 10 mg Placebo Administration route: oral Time of administration: 90 minutes preoperatively
Outcomes	• Tourniquet-related pain by verbal pain score (0 to 10) • Analgesic consumption by fentanyl requirements and diclofenac consumption • Anxiety assessed by verbal anxiety score (0 to 10) (preoperative) • Haemodynamics by mean arterial pressure and heart rate • Onset and recovery of sensory and motor blockade (minutes)
Notes	Sample size calculation: described Study author contacted by email on 15 July 2019 to clarify unspecified issues: no reply

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomly allocated using an online research randomizer..." (page 1422) (Mowafi 2008)
Allocation concealment (selection bias)	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	No reported dropouts or missing data
Selective reporting (reporting bias)	Unclear risk	Study protocol not available

Mowafi 2008 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding of patients, surgeons, or personnel not described
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "all the evaluations were performed by a blinded observer" (page 1423)
Other bias	Low risk	Quote: "the demographic characteristic and surgery times were similar in the two groups" No other sources of bias encountered

Naguib 1999

Study characteristics	
Methods	Randomized, double-blind, placebo-controlled study Location: Saudi Arabia Study design: parallel, 3-armed
Participants	Total of 75 patients randomized 75 patients completed: 25 in melatonin group, 25 in placebo group, 25 in midazolam group Age: melatonin 29.6 (22 to 43), placebo 30.1 (22 to 40), midazolam 29.5 (19 to 44) Gender (M/F) in %: melatonin (0/100), placebo (0/100), midazolam (0/100) ASA class: I Type of surgery: gynaecological laparoscopic procedures Type of anaesthesia: general Baseline (anxiety, pain) described: yes, no
Interventions	Melatonin: 5 mg Midazolam: 15 mg Placebo: saline Administration route: sublingual Time of administration: approximately 100 minutes before induction of anaesthesia
Outcomes	• Anxiety assessed by visual analogue scale (0 to 100) (preoperative and postoperative) • Orientation score (0 to 2) • Sedation score (0 to 4) • Psychomotor activity measured by the Digit Symbol Substitution Test and the Trieger dot test • Amnesia by showing line diagrams

Naguib 1999 *(Continued)*

	• Postoperative pain assessed by visual analogue scale (0 to 100) and morphine consumption (mg)
Notes	Sample size calculation: described Study author contacted by email on 15 July 2019 to clarify unspecified issues - email returned = delivery failure

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "... allocated randomly..." (page 876) (Naguib 1999)
Allocation concealment (selection bias)	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	No reported dropouts or missing data
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "... marked only with a coded label to maintain the double-blind nature of the study" (page 876)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "the same psychologist blinded to group assignment performed all test scoring and calculations" (page 876)
Other bias	Low risk	Quote: "patients in the three groups were comparable in age, weight, height, surgery time and anaesthesia time..." (page 877) No other sources of bias encountered

Naguib 2000

Study characteristics	
Methods	Randomized, double-blind, placebo-controlled study Location: Saudi Arabia Study design: parallel, 3-armed, comparative, dose-response study
Participants	Total of 84 patients randomized 84 patients completed: 36 (12, 12, 12) in melatonin group, 12 in placebo group, 36 (12, 12, 12) in midazolam group Age: melatonin 0.05 mg/kg (30.3 ± 5.6), 0.1 mg/kg (28.4 ± 6.1), 0.2 mg/kg (28.2 ± 6.1) Midazolam: 0.05 mg/kg (23.4 ± 3.9), 0.1 mg/kg (26.2 ± 6.6), 0.2 mg/kg (28.9 ± 6.0) Placebo: 29.8 ± 6.1

Naguib 2000 *(Continued)*

	Gender (M/F) in %: melatonin (0/100), placebo (0/100), midazolam (0/100) ASA class: I Type of surgery: gynaecological laparoscopic procedures Type of anaesthesia: general Baseline (anxiety, pain) described: yes, no
Interventions	Melatonin: 0.05 mg/kg, 0.1 mg/kg, 0.2 mg/kg Placebo: saline Midazolam: 0.05 mg/kg, 0.1 mg/kg, 0.2 mg/kg Administration route: sublingual Time of administration: approximately 100 minutes preoperatively
Outcomes	• Anxiety assessed by visual analogue scale (0 to 100) (preoperative and postoperative) • Orientation score (0 to 2) • Sedation score (0 to 4) • Psychomotor activity measured by the Digit Symbol Substitution Test and the Trieger dot test • Amnesia by showing line diagrams • Postoperative pain assessed by visual analogue scale (0 to 100) and morphine consumption (mg)
Notes	Sample size calculation: described Study author contacted by email on 15 July 2019 to clarify unspecified issues - email returned = delivery failure

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "...randomly allocated..." (page 473) (Naguib 2000)
Allocation concealment (selection bias)	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	No reported dropouts or missing data
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "... marked only with a coded label to maintain the double-blind nature of the study" (page 474) "The contents of the syringe was given sublingually...by a resident not involved in the management of the patient or in the data collection" (page 474)
Blinding of outcome assessment (detection bias)	Low risk	Quote: "The same psychologist blinded to group assignment performed all test scoring and calculations" (page 474)

Naguib 2000 *(Continued)*
All outcomes

Other bias	Low risk	Quote: "Patients in the seven groups were comparable in age, weight, height, surgery time, and anesthesia time..." (page 475) No other sources of bias encountered.

Naguib 2006

Study characteristics	
Methods	Randomized, double-blind, placebo-controlled study Location: Saudi Arabia Study design: parallel, 2-armed
Participants	A total of 200 patients randomized 200 patients completed: melatonin + propofol (MP) (50), melatonin + thiopental (MT) (50), placebo + propofol (PP) (50), placebo + thiopental (PT) (50) Age: MP (32.4 ± 19.9), MT (34.9 ± 8.9), PP (34.4 ± 8.9), PT (31.6 ± 10.9) Gender (M/F) in %: MP (52/48), MT (46/54), PP (30/70), PT (38/62) ASA class: I Type of surgery: not reported Type of anaesthesia: general Baseline (anxiety, pain) described: yes, no
Interventions	Melatonin (0.2 mg/kg) + propofol Melatonin (0.2 mg/kg) + thiopental Placebo + propofol Placebo + thiopental Placebo: saline Administration route: sublingual Time of administration: approximately 50 minutes preoperatively
Outcomes	• Anxiety assessed by visual analogue scale (0 to 100) (preoperative) • Orientation score (0 to 2) • Sedation score (0 to 4) • Induction of anaesthesia assessed by response to verbal command and eyelash reflex
Notes	Sample size calculation: described Study author contacted by email on 15 July 2019 to clarify unspecified issues: email returned = delivery failure

Naguib 2006 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "...according to a computer-generated list" (page 1448) (Naguib 2006)
Allocation concealment (selection bias)	Low risk	Quote: "...the randomization list was maintained by the pharmacy" (page 1448) Quote: "the melatonin... and placebo (saline) solutions were prepared by a pharmacist to a fixed volume of 3 mL in a syringe which the needle had been removed and marked only with a coded label to maintain the double-blind nature of the study" (page 1449)
Incomplete outcome data (attrition bias) All outcomes	Low risk	No reported dropouts or missing data
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "...marked only with a coded label to maintain the double-blind nature of the study" (page 1449) "The contents of the syringe was given sublingually...by a resident not involved in the management of the patient or in the data collection" (page 1449) "The attending anaesthesiologist was unaware of the premedication or induction medication used"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "one investigator blinded to group assignment performed all test scoring in the perioperative period" (page 1449)
Other bias	High risk	Quote: "patients in the four treatment groups were comparable with respect to age, sex distribution, weight, height, premedication-induction time, and time to modified Aldrete scale score of 8..." (page 1449); however overweight females in placebo + propofol and thiopental + propofol groups

Norouzi 2019

Study characteristics	
Methods	Randomized, double-blind, placebo-controlled study Location: Iran Study design: parallel, 2-armed
Participants	Total of 88 patients randomized 88 patients completed: 44 in melatonin group, 44 in placebo group Age: melatonin 43.34 ± 7.69, placebo 44.25 ± 7.16 Gender (M/F): melatonin (21/23), placebo (22/22) ASA class: I to II

Norouzi 2019 *(Continued)*

	Type of surgery: non-emergency abdominal surgery. Surgery time 30 minutes to 1.5 hours Type of anaesthesia: general Baseline (anxiety, pain) described: yes, no
Interventions	Melatonin: 3 mg dissolved in 3 mL distilled water Placebo: 3 mL distilled water Administration route: sublingual Time of administration: 50 minutes before surgery
Outcomes	• Propofol induction dose used to achieve the BIS to lose eyelash reflex and to prevent response to verbal stimulation • Anxiety assessed using a visual analogue scale (VAS) (0 to 100 mm) (measured before premedication, before anaesthesia induction, and during recovery) • Orientation score (0 to 3 scale) same as above • Sedation score (1 to 4 scale) same as above • Haemodynamics (MAP, HR, SaO2, EtCO2)
Notes	Sample size calculation: not described Study author contacted by email 2 October 2019 to clarify unspecified issues: no reply

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "subjects were randomized into two groups…" Missing more information (Norouzi 2019)
Allocation concealment (selection bias)	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Flow diagram (Figure 1) shows that no patients were lost to follow-up
Selective reporting (reporting bias)	High risk	Protocol available. Several more outcomes analysed in the article than mentioned in the protocol (haemodynamics, propofol dose)
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "treatment was implemented by an anesthesiologist resident who was blinded to drugs" Missing more information
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "…data were measured by an anesthesiologist resident, unaware of the groupings…" (page 63)
Other bias	Low risk	Quote: "no significant difference was seen in age between two groups...who were matched for age. They showed no significant difference in gender... and were gender matched" (page 64)

Norouzi 2019 *(Continued)*

	No other sources of bias encountered

Patel 2015

Study characteristics	
Methods	Randomized, double-blind, placebo-controlled study Location: India Study design: parallel, 3-armed
Participants	TA total of 120 patients randomized 109 patients completed: 36 in melatonin group, 37 in midazolam group, 36 in placebo group Age: melatonin 28.78 ± 9.3, midazolam 28.92 ± 9.01, placebo 29.03 ± 9.78 Gender (M/F): melatonin (21/15), midazolam (13/24), placebo (19/17) ASA class: I to II Type of anaesthesia: general Type of surgery: elective surgery Baseline (anxiety, pain) described: yes, no
Interventions	Melatonin: 0.4 mg/kg Midazolam: 0.2 mg/kg Placebo Administration route: oral Time of administration: 60 to 90 minutes before induction of anaesthesia
Outcomes	• Anxiety assessed using visual analogue scale (VAS) (0 = no anxiety, 10 = worst imaginable anxiety) at baseline and 60 to 90 minutes after drug intake • Sedation assessed using a sedation scale (0 to 4) same as above • Orientation assessed using an orientation score (0 to 2) • Cognitive and psychomotor function assessed using DSST and TMT A and B tests
Notes	Sample size calculation: described

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "each patient received either of the drug based on the generated list" (page 38) More information missing (Patel 2015)
Allocation concealment (selection bias)	Unclear risk	Quote: "each patient received either of the drug based on a generated list in thick opaque similar looking envelope..." (page 38)

Patel 2015 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "there were four drop outs in each of the two groups - melatonin and placebo, and three dropouts in the midazolam group mainly because of patients surpassing the stipulated time for induction…" (page 39)
Selective reporting (reporting bias)	Unclear risk	No protocol available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "both patient and the investigator were unaware of the type of drug the patient received" (page 38)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "both patient and the investigator were unaware of the type of drug the patient received" (page 38)
Other bias	High risk	Quote: "the three groups were comparable to each other in terms of age, sex, gender, weight and ASA status" (page 39) However, overweight of males in melatonin group and overweight of females in midazolam group No other sources of bias encountered

Pokharel 2014

Study characteristics	
Methods	Randomized, double-blind, placebo-controlled study Location: Nepal Study design: parallel, 4-armed
Participants	Total of 80 patients randomized 76 patients completed: 19 in group 1 (alprazolam + melatonin), 18 in group 2 (alprazolam), 20 in group 3 (melatonin), 19 in group 4 (placebo) Age: group 1 (38 ± 14), group 2 (37 ± 10), group 3 (34 ± 11), group 4 (36 ± 13) Gender (M/F): group 1 (6/14), group 2 (4/16), group 3 (4/16), group 4 (5/15) ASA class: I to II Type of anaesthesia: general Type of surgery: laparoscopic cholecystectomy Baseline (anxiety, pain) described: yes, no
Interventions	Group 1: 0.5 mg alprazolam + 3 mg melatonin Group 2: 0.5 mg alprazolam Group 3: 3 mg melatonin Group 4: placebo Administration route: oral

Pokharel 2014 *(Continued)*

	Time of administration: 90 minutes before surgery
Outcomes	• Anxiety assessed using a VAS (0 to 100 mm) measured at baseline, 15, 30, and 60 minutes after administration of drug • Sedation assessed using a sedation scale (0 to 4) same as above • Orientation score (0 to 4) assessed before premed and 50 minutes after • Memory 24 hours after surgery assessed by recalling 5 different simple pictures and 2 events.
Notes	Sample size calculation: not described Study author contacted by email on 15 July 2019 to clarify unspecified issues: no reply

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "with the help of computer generated random numbers…patients were assigned to one of the four groups…" (page 2) (Pokharel 2014)
Allocation concealment (selection bias)	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Flow diagram (Figure 1) shows that 4 patients did not complete the study Quote: "…the surgery was postponed in 5 patients because of limited operating room time" (page 3)
Selective reporting (reporting bias)	High risk	In the protocol, researchers state that inclusion criteria are having anxiety VAS > 2 and posted for general anaesthesia with estimated duration < 3 hours. In the article, they have included patients with anxiety VAS > 3 and only patients undergoing laparoscopic cholecystectomy. Also more primary outcomes and measurements are stated in the article than in the protocol
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "similar looking placebo tablets" Quote: "patients were asked to take the study medication…by an investigator not involved in the patient management or data collection" (page 2)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "patients were asked to take the study medication…by an investigator not involved in the patient management or data collection" (page 2)
Other bias	Unclear risk	Quote: "patients in the four groups were comparable in demographic characteristics and perioperative parameters..." (page 3) Appears to be an overweight of females in all groups No other sources of bias encountered

Seet 2015

Study characteristics

Methods	Randomized, double-blind, placebo-controlled study

Seet 2015 *(Continued)*

	Location: Singapore Study design: parallel, 2-armed
Participants	Total of 76 patients randomized 73 patients completed: 38 in melatonin group, 38 in placebo group Age: melatonin 22.7 ± 2.2, placebo 23 ± 2.8 Gender (M/F): melatonin 24/12, placebo 23/14 ASA class: I to II Type of anaesthesia: general Type of surgery: elective extraction of all 4 wisdom teeth Baseline (anxiety, pain) described: yes, yes
Interventions	Melatonin: 6 mg Placebo Administration route: oral Time of administration: 90 minutes before surgery
Outcomes	• Pain assessed using a VAS score (0 to 100 mm) at baseline, 30, 60, 90, 120 minutes, and 4, 24 hours after surgery • Preoperative anxiety assessed using a VAS score (0 to 100) measured at baseline and 30, 60, 90 minutes after administration of study drug • Sleep on first postoperative night assessed using a VAS scale (0 to 100)
Notes	Sample size calculation: described

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "the 76 patients were randomised into two groups with a 1:1 allocation using computer-generated random number codes enclosed in sealed, opaque envelopes" (page 667) (Seet 2015)
Allocation concealment (selection bias)	Low risk	Quote: "the 76 patients were randomised into two groups with a 1:1 allocation using computer-generated random number codes enclosed in sealed, opaque envelopes"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Flow diagram (Figure 1) shows that 3 patients did not complete the trial Quote: "three patients were subsequently excluded after randomisation due to the immediate preoperative decisions by the surgeon to modify procedure and extract additional teeth" (page 667)
Selective reporting (reporting bias)	Unclear risk	No protocol available
Blinding of participants and personnel (performance bias)	Low risk	Quote: "treatment codes for each patient were generated by a research executive who was not participating in the study. The anaesthetist, surgeons, nurses

Seet 2015 *(Continued)*

All outcomes		and data collectors were all blinded to the medication and group assignment until completion of the entire clinical trial"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "...data collectors were all blinded to the medication and group assignment until completion of the entire clinical trial" (page 667)
Other bias	Unclear risk	Quote: "the baseline demographic data between both groups was comparable. Due to referral to hospital from military institutions, there were more male patients than female patients in both the melatonin and placebo groups" No other sources of bias encountered

Torun 2019

Study characteristics	
Methods	Randomized, double-blind, placebo-controlled study Location: Turkey Study design: parallel, 3-armed
Participants	Total of 90 patients randomized 90 patients completed: 30 in melatonin group, 30 in midazolam group, 30 in placebo group Age median (minimum to maximum): melatonin 22 (18 to 38), midazolam 21 (18 to 38), placebo 21 (18 to 32) Gender (M/F): melatonin 7/23, midazolam 3/27, placebo 2/28 ASA class: I to II Type of anaesthesia: local Type of surgery: impacted mandibular third molar surgery (Class IIB by Pell and Gregory classification) Baseline (anxiety, pain) described: yes, no
Interventions	Melatonin: 0.4 mg/kg Midazolam: 0.2 mg/kg Placebo: multi-vitamin tablet Administration route: oral Time of administration: approximately 60 minutes before transport to operating room
Outcomes	• Anxiety assessed using a visual analogue scale (VAS) (0 = no anxiety, 10 = worst imaginable anxiety) preoperatively • Psycomotor and cognitive functions assessed using the Digit Symbol Substitution Test (DSST) and the Trail Making Test (TMT) (preoperatively) • Ramsey Sedation Scale (RSS) every 5 minutes during operation
Notes	Sample size calculated: described

Torun 2019 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "the included patients were randomized by the anesthesiologist using permuted block randomization" (page 2) (Torun 2019)
Allocation concealment (selection bias)	Unclear risk	Quote: "then, all patients were allocated to 1 of 3 groups…" (page 2) Missing more information
Incomplete outcome data (attrition bias) All outcomes	Low risk	No reported dropouts or missing data
Selective reporting (reporting bias)	Unclear risk	No protocol available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "patients, surgeons and assistant medical personnel were blinded to the drugs being administered" (page 2)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "...assistant medical personnel were blinded to the drugs being administered" (page 2)
Other bias	Unclear risk	Qoute: "no relevant differences were observed among groups for age, gender or duration of surgery... VAS, DSST, and TMT-A and -B scores were evaluated before and after premedication. No relevant differences were observed among groups before medication..." (page 3) Appears to be an overweight of females in all groups No other sources of bias encountered

Turkistani 2007

Study characteristics	
Methods	Randomized, double-blind, placebo-controlled study Location: Saudi Arabia Study design: parallel, 3-armed
Participants	Total of 45 patients randomized 45 patients completed: melatonin 3 mg - M3 (15), melatonin 5 mg - M5 (15), no premedication - P (15) Age: M3 32.4 (18 to 47), M5 27.1 (15 to 45), P 30.2 (19 to 41) Gender (M/F) in %: M3 (47/53), M5 (67/33), P (53/47) ASA class: I to II Type of surgery: different surgical procedures Type of anaesthesia: general

Turkistani 2007 *(Continued)*

	Baseline (anxiety, pain) described: yes, no
Interventions	Melatonin 3 mg Melatonin 5 mg No premedication Administration route: oral Time of administration: approximately 100 minutes preoperatively
Outcomes	• Anxiety measured by VAS from 0 to 100 (preoperative) • BIS score (Bispectral Index) • Induction of anaesthesia assessed by response to verbal command and eyelash reflex • Time to be fit for recovery room discharge (minutes) • Heart rate and mean arterial pressure • Induction dose of propofol
Notes	Sample size calculation: described Study author (K.M. Abdullah) contacted by email on 7 October 2019 to clarify unspecified issues: delivery failure

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	Quote: "...using a sealed-envelope technique" (page 400) (Turkistani 2007) Missing more information
Incomplete outcome data (attrition bias) All outcomes	Low risk	No reported dropouts or missing data
Selective reporting (reporting bias)	Unclear risk	Study protocol not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "... an anaesthesiologist, who was blinded to the premedication, injected propofol..."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Other bias	High risk	Quote: "there was no significant differences between the three groups regarding patient characteristics data..." (page 400) Appears to be an overweight of males in group M5

Turkistani 2007 *(Continued)*

No other sources of bias encountered

ASA: American Society of Anesthesiologists physical status classification.
BIS: Bispectral Index.
DSST: Digit Symbol Substitution Test.
EtCO2: end-tidal carbon dioxide.
HR: heart rate.
IOP: intraocular pressure.
IVRA: intravenous regional anaesthesia.
MAP: mean arterial pressure.
PONV: postoperative nausea and vomiting.
SaO2: oxygen saturation.
STAI: State-Trait Anxiety Inventory.
TMT: Trail Making Test.
VAS: visual analogue scale; verbal anxiety score.
VPS: verbal pain score.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Andersen 2014	Intervention was not aimed at treating preoperative and postoperative anxiety
Andersen 2015	Intervention was not aimed at treating preoperative and postoperative anxiety
Bienert 2015	There was neither a placebo nor a benzodiazepine group
Borazan 2010	Intervention was not aimed at treating preoperative or postoperative anxiety
Bourne 2006	Study was not a randomized clinical trial
Cardinali 2002	No surgery was performed in the study
CTRI/2018/02/012032	Intervention was not aimed at treating preoperative or postoperative anxiety
CTRI/2019/08/020502	No placebo or benzodiazepine group was included
de Carvalho 2019	In the study, anxiolysis was measured using the Richmond Agitation-Sedation Scale, which we have assessed as an unfit tool for measuring anxiety
Dwaich 2016	Intervention was not aimed at treating preoperative or postoperative anxiety
Fan 2017	Intervention was not aimed at treating preoperative or postoperative anxiety
Ford 2020	Anxiety was measured too long after intervention
Ghaeli 2015	Intervention was not aimed at treating preoperative or postoperative anxiety
Ghaeli 2018	It was not specified in the study how long after surgery patients received study drug
Gogenur 2009	Intervention was not aimed at treating preoperative or postoperative anxiety
Haddadi 2018	Intervention was not aimed at treating preoperative or postoperative anxiety
Hansen 2014	Treatment with melatonin was given too long preoperatively

Study	Reason for exclusion
Hansen 2014a	Intervention was not aimed at treating preoperative or postoperative anxiety
IRCT20141009019470N82	No placebo or benzodiazepine group was included
IRCT201602147202N10	No surgery was performed
IRCT201701304365N20	Intervention was not aimed at treating preoperative or postoperative anxiety
Ivry 2017	Intervention was not aimed at treating preoperative or postoperative anxiety
Jahromi 2016	Uses the Zhang questionnaire to measure anxiety. We have not been able to find information on this questionnaire. (Study author was contacted by email January 2019; no reply)
Kirksey 2015	Intervention was not aimed at treating preoperative or postoperative anxiety
Madsen 2016	Intervention was not aimed at treating preoperative or postoperative anxiety
Nasr 2014	There was neither a placebo nor a benzodiazepine group
NCT01126294	Study was terminated prematurely and data will not be published (according to first study author - contacted by email July 2013)
NCT02415309	No surgery was performed
NCT02451293	No surgery was performed
NCT03966950	Intervention was not aimed at treating preoperative or postoperative anxiety
Radwan 2010	Intervention was not aimed at treating preoperative or postoperative anxiety
Rokhtabnak 2017	There was neither a placebo nor a benzodiazepine group
Schemmer 2008	Intervention was not aimed at treating preoperative or postoperative anxiety
TCTR20140516001	Intervention was not aimed at treating preoperative or postoperative anxiety
Vij 2018	Intervention was not aimed at treating preoperative or postoperative anxiety
Wawrzyniak 2014	There was neither a placebo nor a benzodiazepine group

ASA: American Society of Anesthesiologists physical status classification.

Characteristics of studies awaiting classification *[ordered by study ID]*

CTRI/2017/08/009245

Methods	Randomized, double-blind, placebo-controlled study - 3-armed
Participants	Total of 60 patients, M/F, ASA I to II, undergoing elective surgery under general anaesthesia
Interventions	• 300 mg gabapentin • 6 mg melatonin • Placebo orally 2 hours before surgery

CTRI/2017/08/009245 *(Continued)*

Outcomes	Attenuation of pressor response to direct laryngoscopy and endotracheal intubation, anxiety level, induction dose of propofol
Notes	Recruitment status complete Study author contacted by email 31 July 2019: no reply

IRCT20160430027677N8

Methods	Randomized, double-blind, placebo-controlled study - 2-armed
Participants	Total of 120 patients, M/F, 50 to 80 years of age, ASA I to III, scheduled for elective cataract surgery with intraocular lens implantation using phacoemulsification for the first time
Interventions	• 3 mg melatonin • Placebo orally 60 minutes before surgery
Outcomes	Verbal anxiety score (VAS), verbal pain score (VPS), intraocular pressure (Schiotz tonometer)
Notes	Recruitment status complete Study author contacted by email 20 September 2019: email delivery failure

ASA: American Society of Anesthesiologists physical status classification.

Characteristics of ongoing studies *[ordered by study ID]*

CTRI/2018/02/011895

Study name	To assess the effect of preoperative melatonin and music on anxiety and recovery profile in patients undergoing day case surgery: a randomized control trial
Methods	Randomized, double-blind, placebo-controlled study - 3-armed
Participants	Total of 99 patients (3 groups), M/F, age 18 to 60 years, ASA I to II, undergoing day case surgery under general anaesthesia
Interventions	Group 1: placebo orally 2 hours before surgery and earphones with music 1 hour before surgery Group 2: 3 mg melatonin orally 2 hours before surgery and earphones without music 1 hour before surgery Group 3: placebo orally 2 hours before surgery and earphones without music 1 hour before surgery
Outcomes	• Preoperative anxiety (no information on scale used to assess anxiety) • Incidence of emergence agitation (Richmond Agitation-Sedation scale) • Postoperative pain scores and rescue analgesics requirement • Incidence of postoperative nausea and vomiting and requirement of rescue agents • Time to attain Modified Aldrette Score 9 • Patient satisfaction score

CTRI/2018/02/011895 *(Continued)*

	• Postoperative anxiety (no information on scale used to assess anxiety)
Starting date	Not yet recruiting
Contact information	Dr Ishwar Bhukal, Department of Anesthesia and Intensive Care, PGIMER, Sector-12, Chandigargh, India
Notes	Study found at WHO trial search Investigator contacted September 2019: no reply

CTRI/2018/04/012960

Study name	Effect of preoperative melatonin on anxiety and pain in patient undergoing phacoemulsification cataract surgery
Methods	Randomized, active-controlled study
Participants	178 patients, M/F, age 50 to 80 years, ASA I to II, undergoing elective phacoemulsification cataract surgery
Interventions	Group 1: melatonin 3 mg orally 90 minutes before surgery Group 2: diazepam 5 mg orally 90 minutes before surgery
Outcomes	• Decrease in verbal anxiety score (VPS) (measured, before premedication, 60 minutes after premedication, during operation, and postoperatively) • Verbal pain score (VPS) • Sedation score • Adverse effects using WHO causality assessment scale
Starting date	27-04-2018
Contact information	N. Sarala, Department of Pharmacology, Sri Devaraj Urs Medical College, Karnataka, India
Notes	Study found at WHO trial search

CTRI/2018/08/015192

Study name	Efficacy of pre-operative oral melatonin on post-operative pain in patients undergoing infra-umbilical surgeries under subarachnoid block - a double-blind randomized control study
Methods	Randomized, double-blind, placebo-controlled study
Participants	70 patients undergoing infra-umbilical surgery under subarachnoid block
Interventions	Group 1: melatonin 3 mg orally (information provided by email correspondence with study author) Group 2: placebo
Outcomes	• Postoperatove pain measured by VAS

CTRI/2018/08/015192 *(Continued)*

	• Perioperative anxiety measured by HAM-A
Starting date	07-08-2018
Contact information	K. Sagar Srinivas Department of Anaesthesiology, Bangalore Medical College and Research Institute, Fort KR Road, Bengaluru
Notes	Study author contacted September 2019: no reply Study found at WHO trial search

CTRI/2018/08/015537

Study name	To assess the effect of oral melatonin premedication on propofol requirement for induction in entropy guided general anaesthesia - a randomized double-blind study
Methods	Randomized, double-blind, placebo-controlled study - 3-armed
Participants	70 patients (3 groups), M/F, 18 to 60 years, ASA I to II, scheduled for surgery under general anaesthesia
Interventions	Group 1: melatonin 3 mg orally Group 2: placebo
Outcomes	• Propofol requirement for induction using entropy • Preoperative anxiety assessed using the Hamilton Anxiety Rating Scale • Preoperative sedation assessed using the Ramsey Sedation Scale (60 minutes after premedication)
Starting date	Not yet recruiting
Contact information	Dr S.S. Nethra, Department of Anaesthesiology, Bangalore Medical College and Research Institute, Fort Karnataka, India
Notes	Study found at WHO trial search

CTRI/2018/10/015917

Study name	Comparison of two separate doses of melatonin as a drug used before anesthesia in cancer patient
Methods	Randomized, placebo-controlled trial - 3-armed
Participants	90 patients (3 groups)
Interventions	Intervention 1: melatonin 0.3 mg/kg Intervention 2: melatonin 0.5 mg/kg Control intervention: placebo Administration route: oral

CTRI/2018/10/015917 *(Continued)*	
	90 minutes before surgery
Outcomes	• Sedation measured using the Ramsey Sedation Scale (90 minutes before surgery and just before surgery) • Anxiety measured using a visual analogue scale (90 minutes before surgery and just before surgery) • Psychomotor function measures using letter cancellation test and Trieger Dot test (90 minutes before surgery and just before surgery) • Orientation (90 minutes before surgery and just before surgery) • Haemodynamic response to intubation
Starting date	Not yet recruiting
Contact information	Namrata Ranaganath, Department of Anesthesiology, Kidwai Cancer Institute, India
Notes	Study found at WHO trial search

CTRI/2019/12/022358	
Study name	Comparing the effects of melatonin with alprazolam to reduce anxiety before surgery and pain after surgery in adults undergoing laparoscopic removal of gall bladder under general anaesthesia
Methods	Randomized, parallel-group trial - 2-armed
Participants	135 patients undergoing laparoscopic cholecystectomy under general anaesthesia
Interventions	Group 1: melatonin 6 mg Group 2: alprazolam 0.5 mg Administration route: oral 120 minutes before surgery
Outcomes	• Preoperative anxiety • Orientation and sedation • Postoperative analgesic pain scores
Starting date	Not yet recruiting
Contact information	Dr Meghana Ravi, M.S. Ramaiah Medical College and Hospitals, Mathikere, Bangalore
Notes	Study found at WHO trial search

CTRI/2020/02/023330	
Study name	A study to evaluate clinical impact of two doses of oral melatonin on preoperative anxiety and postoperative pain relief in patients undergoing orthopaedic surgeries

CTRI/2020/02/023330 *(Continued)*

Methods	Randomized, double-blind, placebo-controlled trial - 3-armed
Participants	63 patients (3 groups) ASA I to III, age 20 to 60 years, undergoing lower limb orthopaedic surgery under spinal anaesthesia
Interventions	Group 1: melatonin 6 mg Group 2: melatonin 3 mg Group 3: placebo Administration route: oral The night before surgery and 1 hour before surgery
Outcomes	• Anxiety • Pain measured using a VAS • Time to first request for analgesic • 72 hours paracetamol and diclofenac sodium consumption • Nausea score and any side effects • Insomnia score • Sedation score
Starting date	Not yet recruiting
Contact information	Dr Narala Sree Vani, Department of Anaesthesiology and Critical Care, Pt. B.D. Sharma, PGIMS, India
Notes	Study found at WHO trial search

IRCT20100707004345N6

Study name	The effect of melatonin on anxiety before hysterectomy
Methods	Randomized, double-blind, placebo-controlled study - 2-armed
Participants	80 patients (2 groups), F only, age 30 to 65 years, elective abdominal hysterectomy
Interventions	Group 1: melatonin 6 mg dissolved in sugar water + lorazepam 1 mg Group 2: sugar water + lorazepam 1 mg
Outcomes	• Anxiety before surgery: measured using a visual analogue scale before drug is prescribed, when patients enter the operating room, and before anaesthetic induction • Blood pressure: measured before drug is prescribed, when patients enter the operating room, and before anaesthetic induction • Heart rate:measured before drug is prescribed, when patients enter the operating room, and before anaesthetic induction
Starting date	05-05-2019

IRCT20100707004345N6 *(Continued)*

Contact information	Ali Mirmansouri, Heshmat Hospital, Rasht, Iran
Notes	Study found at WHO trial search

IRCT20190120042432N1

Study name	Comparison of two oral precursors of melatonin and gabapentin in female candidates for cesarean section under spinal anesthesia
Methods	Randomized, double-blind, placebo-controlled study - 3-armed
Participants	93 patients (3 groups), F only, 18 to 40 years, undergoing elective cesarean section under spinal anaesthesia
Interventions	Group 1: gabapentin 300 mg Group 2: melatonin 3 mg Group 3: placebo Administration route: oral 30 minutes before spinal anaesthesia
Outcomes	• Anxiety and pain: based on the Verbal Anxiety Scale, anxiety and pain levels are measured before premedication, before spinal anaesthesia, 5 minutes after spinal anaesthesia, after exiting the infant, and 15 minutes after spinal anaesthesia, as well as after surgery and patient transmission to recovery • Amount of analgesic drug
Starting date	Recruiting: first enrolment 23 July 2019
Contact information	Yazdi Bijan, Arak University of Medical Sciences, Iran
Notes	Study found at WHO trial search

NCT02386319

Study name	Anxiolytic and analgesic effects of melatonin: a randomized, double-blinded, placebo-controlled clinical study
Methods	Randomized, placebo-controlled trial - 2-armed
Participants	72 patients (2 groups: 36 in each), F, ASA I to II candidates for primary breast surgery or replacement of existing implants
Interventions	Group 1: melatonin 10 mg orally at 9 PM the night before surgery, 120 minutes before surgery, immediately after surgery, at 9 PM the night of surgery Group 2: placebo orally at 9 PM the night before surgery, 120 minutes before surgery, immediately after surgery, at 9 PM the night of surgery
Outcomes	• Integrated pain score during movement assessed using a VAS

NCT02386319 *(Continued)*	• Anxiety assessed using a VAS and STAI • Intraoperative requirement of remifentanil • Intraoperative requirement of propofol • Use of rescue opioids in the ward • Perioperative sleep quality • General well-being and fatigue • Plasma concentrations of melatonin
Starting date	Study consisted of 2 parts: first part measuring melatonin concentration: study complete; second part measuring anxiety and pain: not yet recruiting
Contact information	Dennis Zetner, Herlev Hospital, Denmark
Notes	Study found at ClinicalTrials.gov

ASA: American Society of Anesthesiologists physical status classification.
HAM-A: Hamilton Anxiety Rating Scale.
STAI: State-Trait Anxiety Inventory.
VAS: visual analogue scale; verbal anxiety scale.
VPS: verbal pain scale.
WHO: World Health Organization.

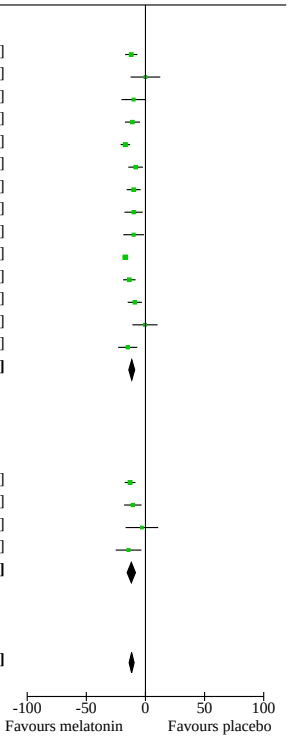
DATA AND ANALYSES

Comparison 1. Melatonin versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Preoperative anxiety (VAS)	18	1264	Mean Difference (IV, Random, 95% CI)	-11.69 [-13.80, -9.59]
1.1.1 Final VAS scores	14	1066	Mean Difference (IV, Random, 95% CI)	-11.58 [-14.08, -9.08]
1.1.2 Change VAS scores	4	198	Mean Difference (IV, Random, 95% CI)	-11.96 [-15.48, -8.45]
1.2 Postoperative anxiety (VAS) [mm]	7	524	Mean Difference (IV, Random, 95% CI)	-5.04 [-9.52, -0.55]
1.2.1 Final VAS scores	5	426	Mean Difference (IV, Random, 95% CI)	-6.04 [-11.69, -0.40]
1.2.2 Change VAS scores	2	98	Mean Difference (IV, Random, 95% CI)	-1.20 [-4.75, 2.35]
1.3 Postoperative anxiety (STAI)	2	73	Mean Difference (IV, Random, 95% CI)	-5.31 [-8.78, -1.84]

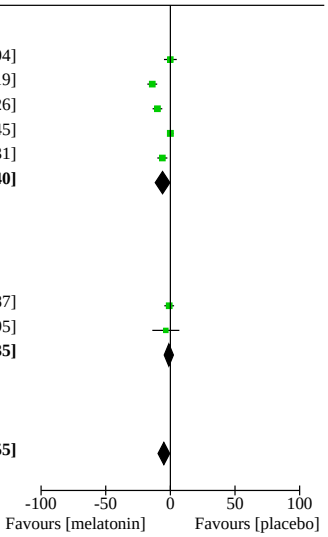
Analysis 1.1. Comparison 1: Melatonin versus placebo, Outcome 1: Preoperative anxiety (VAS)

Study or Subgroup	Melatonin Mean [mm]	Melatonin SD [mm]	Melatonin Total	Placebo Mean [mm]	Placebo SD [mm]	Placebo Total	Weight	Mean Difference IV, Random, 95% CI [mm]
1.1.1 Final VAS scores								
Abbasivash 2019	30	8.1	25	42	10.4	25	7.4%	-12.00 [-17.17 , -6.83]
Capuzzo 2006	30	29.6	67	30	44.4	71	2.3%	0.00 [-12.53 , 12.53]
Ismail 2009	30	7.4	20	40	22.2	20	3.2%	-10.00 [-20.26 , 0.26]
Jain 2019	39	11	30	50	14	30	6.0%	-11.00 [-17.37 , -4.63]
Javaherforooshzadeh 2018	38	7.7	30	55	8.1	30	9.0%	-17.00 [-21.00 , -13.00]
Khare 2018	39	15.3	30	47.3	8.2	30	6.2%	-8.30 [-14.51 , -2.09]
Khezri 2013	30	14.8	30	40	7.4	30	6.5%	-10.00 [-15.92 , -4.08]
Khezri 2013b	20	20	40	30	15	40	4.7%	-10.00 [-17.75 , -2.25]
Mowafi 2008	40	7.4	20	50	18.5	20	4.0%	-10.00 [-18.73 , -1.27]
Naguib 2006	10	5.3	100	27	10.8	100	11.4%	-17.00 [-19.36 , -14.64]
Norouzi 2019	52.9	17.5	44	66.5	3.7	44	7.2%	-13.60 [-18.89 , -8.31]
Patel 2015	33	13	36	42	13	36	6.4%	-9.00 [-15.01 , -2.99]
Seet 2015	22.3	22.7	36	22.7	23.8	37	3.0%	-0.40 [-11.07 , 10.27]
Turkistani 2007	45	17.5	30	60	10	15	4.5%	-15.00 [-23.05 , -6.95]
Subtotal (95% CI)			**538**			**528**	**81.8%**	**-11.58 [-14.08 , -9.08]**
Heterogeneity: Tau² = 11.38; Chi² = 30.72, df = 13 (P = 0.004); I² = 58%								
Test for overall effect: Z = 9.07 (P < 0.00001)								
1.1.2 Change VAS scores								
Naguib 1999	-9	2.9	25	4	11.2	25	8.2%	-13.00 [-17.54 , -8.46]
Naguib 2000	-7.7	11.3	36	3	11.3	12	5.0%	-10.70 [-18.08 , -3.32]
Pokharel 2014	-17	22.3	20	-14	22.2	20	2.0%	-3.00 [-16.79 , 10.79]
Torun 2019	-36.3	22	30	-22	20.7	30	3.0%	-14.30 [-25.11 , -3.49]
Subtotal (95% CI)			**111**			**87**	**18.2%**	**-11.96 [-15.48 , -8.45]**
Heterogeneity: Tau² = 0.00; Chi² = 2.12, df = 3 (P = 0.55); I² = 0%								
Test for overall effect: Z = 6.67 (P < 0.00001)								
Total (95% CI)			**649**			**615**	**100.0%**	**-11.69 [-13.80 , -9.59]**
Heterogeneity: Tau² = 8.74; Chi² = 33.57, df = 17 (P = 0.010); I² = 49%								
Test for overall effect: Z = 10.87 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.86), I² = 0%								



Analysis 1.2. Comparison 1: Melatonin versus placebo, Outcome 2: Postoperative anxiety (VAS) [mm]

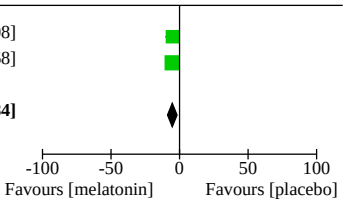
Study or Subgroup	Melatonin Mean	Melatonin SD	Melatonin Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
1.2.1 Final VAS scores								
Capuzzo 2006	0	14.8	67	0	14.8	71	14.1%	0.00 [-4.94 , 4.94]
Javaherforooshzadeh 2018	34	8.1	30	48	6.9	30	15.2%	-14.00 [-17.81 , -10.19]
Khezri 2013	0	7.4	30	10	7.4	30	15.2%	-10.00 [-13.74 , -6.26]
Khezri 2013b	0	2.5	40	0	7.5	40	16.2%	0.00 [-2.45 , 2.45]
Norouzi 2019	21.3	8.2	44	27.5	10.3	44	15.1%	-6.20 [-10.09 , -2.31]
Subtotal (95% CI)			**211**			**215**	**75.9%**	**-6.04 [-11.69 , -0.40]**
Heterogeneity: Tau² = 37.64; Chi² = 48.61, df = 4 (P < 0.00001); I² = 92%								
Test for overall effect: Z = 2.10 (P = 0.04)								
1.2.2 Change VAS scores								
Naguib 1999	-7.4	7.1	25	-6.5	6.5	25	15.2%	-0.90 [-4.67 , 2.87]
Naguib 2000	-8.2	16	36	-4.7	16	12	8.9%	-3.50 [-13.95 , 6.95]
Subtotal (95% CI)			**61**			**37**	**24.1%**	**-1.20 [-4.75 , 2.35]**
Heterogeneity: Tau² = 0.00; Chi² = 0.21, df = 1 (P = 0.65); I² = 0%								
Test for overall effect: Z = 0.66 (P = 0.51)								
Total (95% CI)			**272**			**252**	**100.0%**	**-5.04 [-9.52 , -0.55]**
Heterogeneity: Tau² = 30.74; Chi² = 52.60, df = 6 (P < 0.00001); I² = 89%								
Test for overall effect: Z = 2.20 (P = 0.03)								
Test for subgroup differences: Chi² = 2.03, df = 1 (P = 0.15), I² = 50.7%								



Analysis 1.3. Comparison 1: Melatonin versus placebo, Outcome 3: Postoperative anxiety (STAI)

Study or Subgroup	Melatonin Mean	Melatonin SD	Melatonin Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Caumo 2007	37.3	7.4	17	42.5	7.6	16	45.9%	-5.20 [-10.32 , -0.08]
Caumo 2009	36.8	7.2	20	42.2	8	20	54.1%	-5.40 [-10.12 , -0.68]
Total (95% CI)			**37**			**36**	**100.0%**	**-5.31 [-8.78 , -1.84]**

Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.96); I² = 0%
Test for overall effect: Z = 3.00 (P = 0.003)
Test for subgroup differences: Not applicable

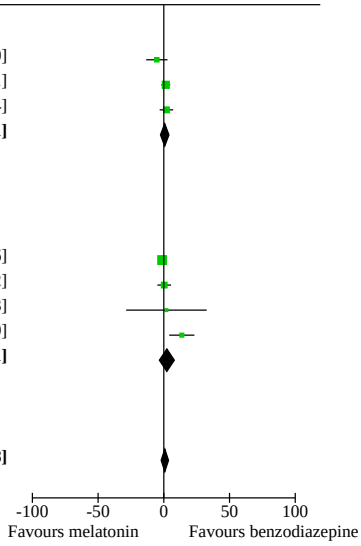


Comparison 2. Melatonin versus benzodiazepine

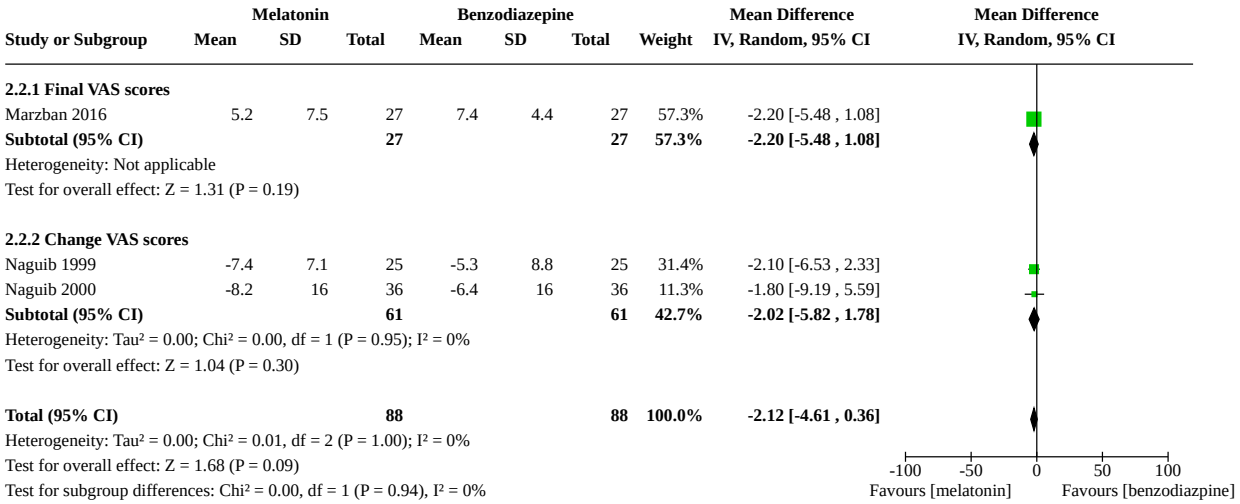
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Preoperative anxiety (VAS) [mm]	7	409	Mean Difference (IV, Random, 95% CI)	0.78 [-2.02, 3.58]
2.1.1 Final VAS scores	3	187	Mean Difference (IV, Random, 95% CI)	0.68 [-2.54, 3.91]
2.1.2 Change VAS scores	4	222	Mean Difference (IV, Random, 95% CI)	2.31 [-3.39, 8.01]
2.2 Postoperative anxiety (VAS) [mm]	3	176	Mean Difference (IV, Random, 95% CI)	-2.12 [-4.61, 0.36]
2.2.1 Final VAS scores	1	54	Mean Difference (IV, Random, 95% CI)	-2.20 [-5.48, 1.08]
2.2.2 Change VAS scores	2	122	Mean Difference (IV, Random, 95% CI)	-2.02 [-5.82, 1.78]

Analysis 2.1. Comparison 2: Melatonin versus benzodiazepine, Outcome 1: Preoperative anxiety (VAS) [mm]

Study or Subgroup	Melatonin Mean	Melatonin SD	Melatonin Total	Benzodiazepine Mean	Benzodiazepine SD	Benzodiazepine Total	Weight	Mean Difference IV, Random, 95% CI
2.1.1 Final VAS scores								
Khare 2018	39	15.3	30	44.3	16.7	30	8.8%	-5.30 [-13.40 , 2.80]
Marzban 2016	13	8.3	27	11.5	3.6	27	22.2%	1.50 [-1.91 , 4.91]
Patel 2015	33	13	36	31	9	37	15.7%	2.00 [-3.14 , 7.14]
Subtotal (95% CI)			**93**			**94**	**46.6%**	**0.68 [-2.54 , 3.91]**
Heterogeneity: Tau² = 1.91; Chi² = 2.54, df = 2 (P = 0.28); I² = 21%								
Test for overall effect: Z = 0.42 (P = 0.68)								
2.1.2 Change VAS scores								
Naguib 1999	-9	2.9	25	-7.7	2.35	25	30.3%	-1.30 [-2.76 , 0.16]
Naguib 2000	-7.7	11.3	36	-8	11.3	36	15.4%	0.30 [-4.92 , 5.52]
Pokharel 2014	-17	37	20	-19	59.3	20	0.8%	2.00 [-28.63 , 32.63]
Torun 2019	-36.3	22	30	-50	15.3	30	6.8%	13.70 [4.11 , 23.29]
Subtotal (95% CI)			**111**			**111**	**53.4%**	**2.31 [-3.39 , 8.01]**
Heterogeneity: Tau² = 18.62; Chi² = 9.43, df = 3 (P = 0.02); I² = 68%								
Test for overall effect: Z = 0.79 (P = 0.43)								
Total (95% CI)			**204**			**205**	**100.0%**	**0.78 [-2.02 , 3.58]**
Heterogeneity: Tau² = 6.19; Chi² = 13.26, df = 6 (P = 0.04); I² = 55%								
Test for overall effect: Z = 0.54 (P = 0.59)								
Test for subgroup differences: Chi² = 0.24, df = 1 (P = 0.63), I² = 0%								



Analysis 2.2. Comparison 2: Melatonin versus benzodiazepine, Outcome 2: Postoperative anxiety (VAS) [mm]



ADDITIONAL TABLES

Table 1. Harms reported in primary study reports

Author, year	Comparison	Harms
Abbasivash 2019	Melatonin, placebo	No harms reported
Acil 2004	Melatonin, midazolam, placebo	"The melatonin group showed increased levels of sedation 90 min after premedication with respect to placebo... This group showed decreased levels of sedation with respect to midazolam..." (page 555) "Furthermore, in the preoperative period, impairment in psychomotor performance was more significant in the midazolam group. In the Trail Making A and B test....the melatonin and midazolam groups exhibited a significantly poorer performance compared with placebo. However, in the Word Fluency test, the midazolam group showed a significant impairment...whereas there was no difference between the scores of the melatonin and placebo groups... The placebo group showed better postoperative performance on the Word Fluency test. Amnesia was only significant in the midazolam group..." (page 556) No harms reported
Capuzzo 2006	Melatonin, placebo	No harms reported
Caumo 2007	Melatonin, placebo	No harms reported
Caumo 2009	Melatonin, clonidine, placebo	No harms reported
Dianatkhah 2015	Melatonin, oxazepam	"A smaller proportion of the participants experience delirium in the melatonin group (n=4, 0.06%) than in the oxazepam group (n=9, 0.12%), but this difference was not statistically significant (P value = 0.187)" (page 125) No harms reported

Table 1. Harms reported in primary study reports *(Continued)*

Hoseini 2015	Melatonin, clonidine, gabapentin, placebo	No harms reported; however, the frequency of vomiting and the severity of nausea were measured, and no differences between groups were observed (Table 3) (page 123)
Ionescu 2008	Melatonin, midazolam, placebo	"Amnesia scores, assessed as the number of remembered pictures, were significantly better (the score of the remembered pictures was greater) in the melatonin group in comparison to the midazolam group at every evaluation time, whereas there were no significant difference between the melatonin and placebo groups" (page 11) "No side effects of melatonin were noted" (page 10)
Ismail 2009	Melatonin, placebo	"Contraray to the control group, MAP decreased significantly after melatonin premedication. No incidence of hypotension or bradycardia requiring intervention was reported in groups...One patient in the melatonin group complained of dizziness, and another patient in control group suffered nausea" (page 1148)
Jain 2019	Melatonin, placebo	"In our study, there were no untoward incidences of bradycardia, cardiac arrhythmias, respiratory depression, nausea, hypotension, anaphylaxis, and drug interactions, in any of the groups" (page 20)
Javaherforooshzadeh 2018	Melatonin, gabapentin, placebo	"In this study, a single dose of gabapentin was used, thus, patients did not report any side effects. Ismail et al. found that MAP was significantly reduced after melatonin premedication, although it was described that this difference, at some points, was unimportant between the groups and was consistent with our results" (page 5)
Khanna 2019	Melatonin, pregabalin, alprazolam	"In or study we found that patients in group M were more sedated as compared to group P or group A at all intervals, and the difference at all intervals was statistically significant, whereas sedation score in patients of group P and group A was comparable at all intervals, and the difference at all intervals was statistically insignificant" (page 70) "Side effects like headache, dizziness were comparable in all groups..." (page 70)
Khare 2018	Melatonin, alprazolam, placebo	"Our results showed that both melatonin and alprazolam caused significant sedation in patients as compared to placebo. Among Group M and Group A, melatonin caused less sedation than alprazolam" (page 661) "In our study, alprazolam caused change in orientation score in patients when compared to melatonin and placebo groups...There was a decline in cognitive function in Group A as compared to Group P, whereas the cognitive function was enhanced or maintained in Group M..." (pages 661-662) No harms reported
Khezri 2013	Melatonin, placebo	"No patient developed hypoxia, hypotension, or bradycardia. Only one patient in the melatonin group complained of a mild headache" (page 322)
Khezri 2013b	Melatonin, gabapentin, placebo	"Significant differences were observed between sedation scores during RBB placement in gabapentin and placebo groups. The difference in sedation scores during RBB placement in melatonin versus gabapentin and placebo was insignificant" (page 584) "No patient developed hypoxia, hypotension, bradycardia, excessive drowsiness (or sleepiness), nausea, and vomiting during surgery. One patient in the melatonin group complained of mild headache, and one in the gabapentin group of severe dizziness while staying in the ward" (page 584)

Table 1. Harms reported in primary study reports *(Continued)*

Khezri 2016	Melatonin, melatonin, placebo	"As shown in Table 3, apart of headache, no significant differences were found in the three groups in terms of other intraoperative and postoperative side effects including pruritus, nausea, vomiting, and respiratory depression. The incidence of headache in group M_6 was significantly higher than other groups" (page 966) "All newborns in our study were free of any adverse effect" (page 967)
Marzban 2016	Melatonin, gabapentin, placebo (midazolam)	Views sedation No harms reported
Mowafi 2008	Melatonin, placebo	"Melatonin premedication reduced MAP compared to control group... No incidence of hypotension or bradycardia requiring intervention was reported in either group" (page 1424) One patient complained of dizziness and two in the melatonin group had excessive sleepiness" (page 1424)
Naguib 1999	Melatonin, midazolam, placebo	"Patients who received midazolam and melatonin showed increased levels of sedation at 60 and 90 min... Furthermore, patients in the midazolam group showed significantly (P<0.05) higher levels of sedation compared with the melatonin group at 30 and 60 min after premedication..," (page 877) "However, in the preoperative period only patients in the midazolam group experienced significant impairment of psychomotor skills. After operation, patients who received midazolam or melatonin had increased levels of sedation at 30 min and impairment of performance of the DSST... Amnesia was notable only in the midazolam group for one preoperative event" (pages 878-879) "No side effects were noted" (page 878)
Naguib 2000	Melatonin, midazolam, placebo	"...patients who received premedication with 0.05, 0.1 or 0.2 mg/kg sublingual midazolam or melatonin had a significant decrease in anxiety levels (Figure 1) and increase levels of sedation preoperatively... After operation, patients who received 0.2 mg/kg midazolam premedication had increased levels of sedation at 90 min compared with the 0.05 and 0.1 mg/kg melatonin groups" (pages 877-878) "However, in the preoperative period, only patients in the three midazolam groups experiences significant impairment in psychomotor skills... In addition, patients in the three midazolam groups had impairment of performance on the DSST at 15, 30, 60, and 90 minutes postoperatively... Amnesia was notable only with the 0.2 mg/kg midazolam group for two preoperative events" (pages 477-478) "No side-effects were noted" (page 477)
Naguib 2006	Melatonin, placebo	"Here, oral premedication with 0.2 mg/kg melatonin approximately 50 min before induction of anaesthesia significantly reduced preoperative anxiety and increased sedation without impairment of orientation..." (page 1450) No harms reported
Norouzi 2019	Melatonin, placebo	"In addition, no significant difference was found in orientation between both before melatonin administration and in recovery (P>0.05), while it was statistically significant before anesthesia induction (P=0.44) and lower in the melatonin group before induction... In addition, there was no significant difference in sedation between the two groups..." (pages 64-65)

Table 1. Harms reported in primary study reports *(Continued)*

		"The results of this double-blinded clinical trial showed that MAP was lower in the melatonin group..." (page 65) No harms reported
Patel 2015	Melatonin, midazolam, placebo	"This showed that psychomotor and cognitive functions were not affected in melatonin group patients whereas they were significantly affected in midazolam group patients... This showed that midazolam produced the maximum derangement in both psychomotor and cognitive functions after premedication and before surgery" (pages 39-40) "The intergroup comparison of sedation scores showed that midazolam produced the highest degree of sedation when compared to melatonin and placebo. Melatonin also showed sedative properties when compared with placebo" (page 41) No harms reported
Pokharel 2014	Melatonin, alprazolam, melatonin + alprazolam, placebo	"In our patients, alprazolam produced more sedation scores than placebo at 60 min after premedication, but the difference was not statistically significant. However, our patients who received alprazolam got sedated half an our earlier than placebo... We too found that the melatonin administration was associated with earlier onset of sleep than placebo" (pages 3-4) "More number of patients in groups receiving the combination drugs and alprazolam (9 each) did not recognize the picture shown at 60 min after premedication...Amnesia for two events was notable in maximum number of patients in the group receiving the combination of alprazolam and melatonin. However the difference was statistically significant only between groups receiving combination drugs (5 (26%)) and placebo (0) for only one event" (page 3) "There was no statistical difference between the groups in the number of people reporting occurrence of nausea, vomiting, dizziness, headache, or restlessness (Table 1)" (page 3)
Seet 2015	Melatonin, placebo	No harms reported
Torun 2019	Melatonin, midazolam, placebo	"Although sedation levels were considerably higher in the melatonin group than in the placebo group at 25, 30, and 35 minutes, during this increase, patient RSS scores did not exceed 3 and did not affect cognitive or psychomotor functions. No side effects were encountered" (page 6)
Turkistani 2007	Melatonin, melatonin, no premedication (placebo)	No harms reported

DSST: Digit Symbol Substitution Test.
MAP: mean arterial pressure.
RBB: retrobulbar block.
RSS: Ramsey Sedation Scale.

Table 2. Sensitivity analysis - primary and secondary outcomes - exclusion of studies with an overall high risk of bias

Outcomes	Statistical method	Studies	Participants	Effect estimate (I^2)

Table 2. Sensitivity analysis - primary and secondary outcomes - exclusion of studies with an overall high risk of bias *(Continued)*

Preoperative anxiety VAS [mm] - melatonin vs placebo **- excluding studies with an overall high risk of bias**	MD (IV, Random, 95% CI)	13	936	-11.20 (-13.87 to -8.53) (54%)
Final VAS scores	MD (IV, Random, 95% CI)	10	778	-10.49 (-13.97 to -7.00) (65%)
Change VAS scores	MD (IV, Random, 95% CI)	3	158	-12.59 (-16.23 to -8.95) (0%)
Postoperative anxiety VAS [mm] - melatonin vs placebo **- excluding studies with an overall high risk of bias**	MD (IV, Random, 95% CI)	3	236	-0.79 (-3.67 to 2.09) (0%)
Final VAS scores	MD (IV, Random, 95% CI)	1	138	0.00 (-4.94 to 4.94) (-)
Change VAS scores	MD (IV, Random, 95% CI)	2	98	-1.20 (-4.75 to 2.35) (0%)
Preoperative anxiety VAS [mm] - melatonin vs benzodiazepine **- excluding studies with an overall high risk of bias**	MD (IV, Random, 95% CI)	5	315	0.85 (-3.01 to 4.72) (66%)
Final VAS scores	MD (IV, Random, 95% CI)	2	133	-0.95 (-7.97 to 6.07) (55%)
Change VAS scores	MD (IV, Random, 95% CI)	3	182	2.49 (-3.68 to 8.66) (79%)
Postoperative anxiety VAS [mm] - melatonin vs benzodiazepine **- excluding studies with an overall high risk of bias**	MD (IV, Random, 95% CI)	2	122	-2.02 (-5.82 to 1.78) (0%)

CI: confidence interval.
IV: inverse variance.
MD: mean difference.
SD: standard deviation.
VAS: visual analogue scale.

Table 3. Primary and secondary outcomes as reported in the primary study reports

Author, year	Preoperative VAS	Preoperative STAI	Preoperative anxiety HAM-A	Preoperative BAI	Postoperative VAS	Postoperative STAI	Postoperative HAM-A	Postoperative BAI
Abbasivash 2019	↓ (90 min after premed) compared to placebo	NM	NM	NM	NM	NM	NM	NM
Acil 2004	↓ (90 min after premed) compared to placebo → (90 min after premed) compared to midazolam	NM	NM	NM	↓ (90 min postop) compared to placebo ↓ (90 min postop) compared to midazolam	NM	NM	NM
Capuzzo 2006	→ (90 min after premed) compared to placebo	NM	NM	NM	→ (in recovery room) compared to placebo	NM	NM	NM
Caumo 2007	NM	NM	NM	NM	NM	↓ (6 h postop) compared to placebo	NM	NM
Caumo 2009	NM	NM	NM	NM	NM	↓ (6 h postop) compared to placebo → (6 h postop) compared to clonidine	NM	NM
Dianatkhah 2015	NM	NM	→ (before surgery) compared to oxazepam	NM	NM	NM	↓ (after surgery) compared to oxazepam	NM
Hoseini 2015	NM	→ (120 min after premed) compared to placebo	NM	NM	NM	NM	NM	NM

Table 3. Primary and secondary outcomes as reported in the primary study reports *(Continued)*

		→ (120 min after premed) compared to clonidine → (120 min after premed) compared to gabapentin						
Ionescu 2008	NM	→ (90 min after premed) compared to placebo → (90 min after premed) compared to midazolam	NM	NM	NM	↓ (1,6 and 24 h postop) compared to placebo) ↓ (1 h and 24 h postop) compared to midazolam → (6 h postop) compared to midazolam	NM	NM
Ismail 2009	↓ (90 min after premed) compared to placebo	NM	NM	NM	NM	NM	NM	NM
Jain 2019	↓ (120 min after premed) compared to placebo	NM	NM	NM	NM	NM	NM	NM
Javaher-forooshzadeh 2018	↓ (85 min after premed) compared to placebo → (85 min after premed) compared to gabapentin	NM	NM	NM	↓ (1 h after arrival to recovery room) compared to placebo ↓ (6 h after arrival to recovery room) compared to placebo	NM	NM	NM

Table 3. Primary and secondary outcomes as reported in the primary study reports *(Continued)*

					→ (6 h after arrival to recovery room) compared to gabapentin			
Khanna 2019	NM	NM	NM	→ (60 min after premed) compared to pregabalin → (60 min after premed) compared to alprazolam	NM	NM	NM	→ (1, 2, 6, 12 hours after surgery) compared to pregabalin → (1, 2, 6, 12 hours after surgery) compared to alprazolam
Khare 2018	↓ (120 min after premed) compared to placebo → (120 min after premed) compared to alprazolam	NM	NM	NM	NM	NM	NM	NM
Khezri 2013	↓ (60 min after premed) compared to placebo	NM	NM	NM	↓ (before discharge from recovery room) compared to placebo	NM	NM	NM
Khezri 2013b	↓ (90 min after premed) compared to placebo → (90 min after premed) compared to gabapentin	NM	NM	NM	↓ (postoperative before discharge) compared to placebo → (postoperative before discharge) compared to gabapentin	NM	NM	NM
Khezri 2016	↓ (20 min after premed) compared to placebo	NM	NM	NM	→ (in recovery room) compared to placebo	NM	NM	NM
Marzban 2016	→ (90 min after premed) compared to placebo/midazolam → (90 min after premed) compared to gabapentin	NM	NM	NM	→ (in recovery room) compared to placebo/midazolam	NM	NM	NM

Table 3. Primary and secondary outcomes as reported in the primary study reports *(Continued)*

					→ (in recovery room) compared to gabapentin)			
Mowafi 2008	↓ (90 min after premed) compared to placebo	NM	NM	NM	NM	NM	NM	NM
Naguib 1999	↓ (90 min after premed) compared to placebo → (90 min after premed) compared to midazolam	NM	NM	NM	→ (90 min postop) compared to placebo → (90 min postop) compared to midazolam	NM	NM	NM
Naguib 2000	↓ (90 min after premed) compared to placebo → (90 min after premed) compared to midazolam	NM	NM	NM	→ (90 min postop) compared to placebo → (90 min postop) compared to midazolam	NM	NM	NM
Naguib 2006	↓ (50 min after premed) compared to placebo	NM	NM	NM	NM	NM	NM	NM
Norouzi 2019	↓ (50 min after premed) compared to placebo	NM	NM	NM	↓ (in recovery room) compared to placebo	NM	NM	NM
Patel 2015	↓ (60 to 90 min after premed) compared to placebo → (60 to 90 min after premed) compared to midazolam	NM	NM	NM	NM	NM	NM	NM
Pokharel 2014	→ (60 to 90 min after premed) compared to placebo → (60 to 90 min after premed) compared to alprazolam	NM	NM	NM	NM	NM	NM	NM
Seet 2015	→ (30 to 60 min after premed) compared to placebo	NM	NM	NM	NM	NM	NM	NM
Torun 2019	↓ (60 min after premed) compared to placebo	NM	NM	NM	NM	NM	NM	NM

Table 3. Primary and secondary outcomes as reported in the primary study reports *(Continued)*

	→ (60 min after premed) compared to midazolam							
Turkistani 2007	↓ (approximately 100 min after premed) compared to placebo	NM	NM	NM	NM	NM	NM	NM

→: no difference between groups.
↓: lower, difference compared to placebo or midazolam.
BAI: Beck Anxiety Inventory.
HAM-A: Hamilton Anxiety Rating Scale.
NM: not measured.
STAI: State Trait Anxiety Inventory.
VAS: visual analogue scale.

Table 4. Sensitivity analysis - primary and secondary outcomes

Outcome	Statistical method	Studies	Participants	Effect estimate (I^2)
Preoperative anxiety VAS [mm] - melatonin vs placebo **- excluding studies not reporting outcome in mean (SD)**	MD (IV, Random, 95% CI)	10	621	-11.90 (-14.24 to -9.55) (34%)
Final VAS scores	MD (IV, Random, 95% CI)	7	463	-11.34 (-14.62 to -8.06) (55%)
Change VAS scores	MD (IV, Random, 95% CI)	3	158	-12.59 (-16.23 to -8.95) (0%)
Postoperative anxiety VAS [mm] - melatonin vs placebo **- excluding studies not reporting outcome in mean (SD)** **or reporting SD values of zero**	MD (IV, Random, 95% CI)	4	246	-4.31 (-7.18 to -1.44) (39%)
Final VAS scores	MD (IV, Random, 95% CI)	2	148	-6.09 (-8.74 to -3.44) (0%)
Change VAS scores	MD (IV, Random, 95% CI)	2	98	-1.20 (-4.75 to 2.35) (0%)
Preoperative anxiety VAS [mm] - melatonin vs benzodiazepine **- excluding studies not reporting outcome in mean (SD) and** **an additional study due to lack of blinding**	MD (IV, Random, 95% CI)	5	315	0.91 (-3.02 to 4.38) (67%)
Final VAS scores	MD (IV, Random, 95% CI)	2	133	-0.95 (-7.97 to 6.07) (55%)
Change VAS scores	MD (IV, Random, 95% CI)	3	182	2.61 (-3.68 to 8.90) (80%)

CI: confidence interval.
IV: inverse variance.
MD: mean difference.
SD: standard deviation.
VAS: visual analogue scale.

Table 5. Subgroup analysis - preoperative anxiety - melatonin vs placebo

Outcome	Statistical method	Studies	Participants	Effect estimate (I^2)	Test for subgroup differences (P)
Anaesthetic modality	MD (IV, Random, 95% CI)	17	1136	-12.13 (-14.00 to -10.26) (31%)	0.52
General anaesthesia	MD (IV, Random, 95% CI)	11	796	-12.25 (-14.85 to -9.64) (51%)	
Spinal, regional, or topical anaesthesia	MD (IV, Random, 95% CI)	6	340	-10.97 (-13.91 to -8.02) (0%)	
Age of participants	MD (IV, Random, 95% CI)	17	1184	-11.78 (-13.99 to -9.85) (50%)	0.16
Age > 60 years	MD (IV, Random, 95% CI)	3	258	-8.04 (-13.58 to -2.50) (0%)	
Age ≤ 60 years	MD (IV, Random, 95% CI)	14	946	-12.36 (-14.62 to -10.09) (50%)	
Dose of melatonin	MD (IV, Random, 95% CI)	17	1216	-11.71 (-13.91 to -9.50) (52%)	0.54
Melatonin dose ≥ 6 mg	MD (IV, Random, 95% CI)	10	735	-12.28 (-15.21 to -9.35) (57%)	
Melatonin dose < 6 mg	MD (IV, Random, 95% CI)	7	481	-10.98 (-13.88 to -8.09) (22%)	

CI: confidence interval.
IV: inverse variance.
MD: mean difference.
ST: standard deviation.
VAS: visual analogue scale.

APPENDICES

Appendix 1. Search strategy for CENTRAL, the Cochrane Library

#1 MeSH descriptor: [Melatonin] explode all trees
#2 Melatonin or "N-acetyl-5-methoxytryptamine"
#3 (#1 OR #2)
#4 MeSH descriptor [Anxiety] explode all trees
#5 MeSH descriptor [Preoperative Care] explode all trees
#6 MeSH descriptor [Preoperative Period] explode all trees

#7 MeSH descriptor [Anesthesia Recovery Period] explode all trees

#8 MeSH descriptor [Premedication] explode all trees

#9 MeSH descriptor: [Postoperative Care] explode all trees

#10 MeSH descriptor [Postoperative Period] explode all trees

#11 (preoperat* or (pre NEAR/1 operat*) or (pre NEAR/1 procedur*) or preprocedur* or (pre NEAR/1 surg*) or presurg* or anxiet* or premedication* or (pre NEAR/1 medication*) or (before NEAR/2 (surg* or procedur*))) or (pain* or (analg* NEAR/3 treatment) or (postoperat* or post operat* or post surg* or postsurg* or post procedur* or postprocedur*)):ti,ab
#12 (#4 OR #5 OR #6 OR #7 or #8 or #9 or #10 or #11)
#10 (#3 AND #12)

Appendix 2. Search strategy for MEDLINE (OvidSP)

1. exp Melatonin/ or Melatonin.af. or N-acetyl-5-methoxytryptamine.mp.

2. exp anxiety/ or preoperative period/ or preoperative care/ or exp anesthesia recovery period/ or premedication/ or postoperative period/ or postoperative care/ or (preoperat* or pre operat* or pre procedur* or preprocedur* or pre surg* or presurg* or anxiet* or (before adj2 (surg* or procedur*))).af. or pain*.ti,ab. or (analg* adj3 treatment).mp. or (postoperat* or post operat* or post surg* or postsurg* or post procedur* or postprocedur*).ti,ab. or (premedication* or pre-medication*).af.
3. ((randomized controlled trial or controlled clinical trial).pt. or random*.ab. or placebo.ab. or drug therapy.fs. or trial.ab. or groups.ab.) not (animals not (humans and animals)).sh.
4. 1 and 2 and 3

Appendix 3. Search strategy for Embase (OvidSP)

1 exp Melatonin/ or Melatonin.af. or N-acetyl-5-methoxytryptamine.mp.

2. exp anxiety/ or preoperative treatment/ or preoperative period/ or preoperative care/ or postanesthesia care/ or postoperative analgesia/ or premedication/ or postoperative period/ or postoperative care/ or (preoperat* or pre operat* or pre procedur* or preprocedur* or pre surg* or presurg* or anxiet* or (before adj2 (surg* or procedur*))).af. or pain*.ti,ab. or (analg* adj3 treatment).mp. or (postoperat* or post operat* or post surg* or postsurg* or post procedur* or postprocedur*).ti,ab. or (premedication* or pre-medication*).af.

3. ((crossover procedure or double blind procedure or single blind procedure).sh. or (crossover* or cross over*).ti,ab. or placebo*.ti,ab,sh. or (doubl* adj blind*).ti,ab. or (controlled adj3 (study or design or trial)).ti,ab. or allocat*.ti,ab. or trial*.ti,ab. or randomized controlled trial.sh. or random*.ti,ab. or groups.ti,ab.) not ((exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti,ab.))

4. 1 and 2 and 3

Appendix 4. Search strategy for CINAHL (EBSCO host)

S1. (MM "Melatonin") OR TX Melatonin or N-acetyl-5-methoxytryptamine
S2. (MM "Anxiety+") OR (MH "Preoperative Care") OR (MH "Preoperative Period") OR (MH "Postoperative Care") OR (MH "Premedication") OR (MH "Postoperative Period")) or TX (pre operat* or preoperat* or anxiet* or presurg* or pre surg* or preprocedur* or pre procedur* or (before N2 (surg* or procedur*))) or AB pain* or AB (analg* and treatment) or TX (postoperat* or post operat* or postsurg* or post surg* or post procedur* or postprocedur*) OR TX (premedication* or pre medication*)
S3. S1 AND S2

Appendix 5. Search strategy for ISI Web of Science

#1 TS=(Melatonin or N-acetyl-5-methoxytryptamine)
#2 TS=(preoperat* or (pre NEAR/1 operat*) or presurg* or (pre NEAR/1 surg*) or preprocedur* or (pre NEAR/1 procedur*) or anxiet*) or TS=(analg* NEAR treatment) or TS=(postoperat* or (post NEAR/1 operat*) or postsurg* or (post NEAR/1 surg*) or postprocedur* or (post NEAR/1 procedur*)) or TI=pain* or TS=(premedication* or (pre NEAR/1 medication*)) or TS=(before NEAR/2 (surg* or procedur*))
#3 TS=clinical trial* OR TS=research design OR TS=comparative stud* OR TS=evaluation stud* OR TS=(controlled NEAR (trial* or stud*)) OR TS=follow-up stud* OR TS=prospective stud* OR TS=random* OR TS=placebo* OR TS=((single or double or triple or treble) or (mask* or blind*)) OR TS=multicenter

#4 (#1 and #2 and #3)

WHAT'S NEW

Date	Event	Description
10 July 2020	New search has been performed	This is an update of Hansen 2015. We searched the following databases on 22 November 2019: CENTRAL, MEDLINE, Embase, CINAHL, and Web of Science. For ongoing trials and protocols, we searched clinicaltrials.gov, Current Controlled Trials, and the World Health Organization (WHO) International Clinical Trials Registry Platform. We re-ran the search on 10 July 2020. We included 27 studies, 12 of which were also included in the previous review. We updated the conclusions
10 July 2020	New citation required and conclusions have changed	This is an update of Hansen 2015. We included 27 studies, 12 of which were also included in the previous review. We explored immediate and delayed postoperative anxiety. We updated the GRADE assessment and added new 'Summary of findings' tables. We performed subgroup analysis to explore heterogeneity. Conclusions changed: contrary to the previous review, we found an effect of melatonin compared with placebo on immediate and delayed postoperative anxiety; however the evidence was uncertain.

HISTORY

Protocol first published: Issue 5, 2012
Review first published: Issue 4, 2015

Date	Event	Description
9 February 2017	Amended	Plain language summary: we clarified that age range referred to the age of participants in the studies

CONTRIBUTIONS OF AUTHORS

Conceiving the review: Dennis Zetner (DZ), Ann Merete Møller (AMM), Jacob Rosenberg (JR).

Co-ordinating the review: Bennedikte Kollerup Madsen (BKM).

Undertaking manual searches: BKM.

Screening search results: BKM, DZ.

Organizing retrieval of papers: BKM.

Screening retrieved papers against inclusion criteria: BKM.

Appraising quality of papers: BKM, NJ (Negar Jamshidi).

Abstracting data from papers: BKM, NJ.

Writing to/calling authors of papers for additional information: BKM.

Providing additional data about papers: BKM.

Obtaining and screening data on unpublished studies: BKM.

Managing data for the review: BKM.

Entering data into Review Manager (RevMan 5.3): BKM.

Analysing RevMan statistical data: BKM.

Performing other statistical analyses not using RevMan: BKM.

Interpretatinf data: BKM.

Making statistical inferences: BKM.

Writing the review: BKM, DZ, AMM, JR.

Securing funding for the review: JR.

Performing previous work that was the foundation of the present study: IG (Ismail Gögenur), MVH (Melissa V Hansen), NLH (Natalie L Halladin), AMM, JR.

Serving as guarantor for the review (one author): BKM.

Taking responsibility for reading and checking the review before submission: BKM.

DECLARATIONS OF INTEREST

B. Madsen: none known.

A. Møller: none known.

J. Rosenberg: none known.

D. Zetner: has received a PhD grant from RepoCeuticals ApS. RepoCeuticals ApS had no involvement with the Cochrane Review and has not in any way been able to influence this process.

SOURCES OF SUPPORT

Internal sources

- No support provided, Other

  None

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This is an update of a previous review (Hansen 2015). We have not changed the protocol for this update, so differences between the previous review and the protocol are still current. We have added differences between the protocol and this current review to the list presented below.

The original intention - Hansen 2012 - of the previous review - Hansen 2015 - was to clarify whether melatonin could be a worthy alternative and potentially substitute use of the standard, anxiolytic premedication treatment with benzodiazepines, with all its known disadvantages. During the phase from development of the protocol to writing of the review, the review author team realized that pain and anxiety are related but that the exact pathophysiological mechanisms are not entirely clear and treatment strategies for the two entities are different. They chose to focus only on melatonin's anxiolytic effect in the perioperative period, explaining why they removed two secondary outcomes (pain and analgesic treatment). In the present updated review, we chose to keep this strategy.

Specific changes include the following.

TITLE

- We have changed the title to "Melatonin for preoperative and postoperative anxiety in adults", thereby covering the objectives.

BACKGROUND

- We have added two paragraphs about postoperative anxiety under "Description of the condition" and have added a few sentences under "Why it is important to do this review".

OBJECTIVES

- We have added postoperative anxiety to cover the entire perioperative period.

METHODS

- We have added postoperative anxiety to the paragraph under "Types of studies". We have also added that we intended to include cluster-randomized studies.
- We have added topical anaesthesia to the "Types of participants".
- Under "Types of outcome measures", the secondary outcomes pain and analgesic treatment have been omitted.
- Under "Types of outcome measures", we decided to divide postoperative anxiety into immediate and delayed postoperative anxiety, and we specified what we regarded as the preoperative period. We also specified that no restrictions were made regarding how long after premedication preoperative anxiety had to be assessed.
- Under "Data extraction and management", we state that two review authors will perform data extraction; however, for this update, one review author performed data extraction twice.
- Under "Measures of treatment effect", as we did not have categorical data, we omitted the sentence "we will present categorical data..."
- Under "Measures of treatment effect", regarding number needed to treat for an additional beneficial outcome (NNTB) and number needed to treat for an additional harmful outcome (NNTH), it was not possible to calculate these; therefore we deleted the sentence.
- Under "Unit of analysis issues", we have added information regarding how we intended to include cluster-randomized trials in meta-analysis, and how we intended to deal with unit of analysis problems.
- We changed the phrasing in "Assessment of heterogeneity" to suit the heterogeneity we found in the included studies.
- As we did not have dichotomous data, we changed the wording under "Data synthesis" accordingly. We added a new reference comparing NRS with VAS. We also added detailed information on data synthesis according to the included studies.
- As we have omitted two of the secondary outcomes, we have adapted the "Summary of findings tables" text to the relevant outcomes.
- We have changed to the correct initials of authors in the data extraction and management paragraph and in the assessment of risk of bias paragraph.
- We have changed the RevMan version to the newest version available.
- We have performed sensitivity analysis on our primary and secondary outcomes.

INDEX TERMS

Medical Subject Headings (MeSH)

Alprazolam [therapeutic use]; Anti-Anxiety Agents [adverse effects] [*therapeutic use]; Anxiety [*drug therapy]; Bias; Clonidine [therapeutic use]; Drug Administration Schedule; Melatonin [adverse effects] [*therapeutic use]; Midazolam [therapeutic use]; Oxazepam [therapeutic use]; Postoperative Care; Postoperative Complications [drug therapy] [psychology]; Preoperative Care; Publication Bias; Randomized Controlled Trials as Topic; Surgical Procedures, Operative [*psychology]

MeSH check words

Adult; Aged; Aged, 80 and over; Humans; Middle Aged